RESULT 24
AAY25113
ID AAY25113 standard; protein; 684 AA.
XX
AC AAY25113;
XX
DT 25-AUG-1999 (first entry)
XX
DE Human alpha1 (XVIII) collagen protein.
XX
KW Alpha1(XVIII) collagen; mimetic; endostatin; atomic coordinate; library;
KW anti-angiogenic; heparin binding domain; receptor binding domain; mimic;
KW alpha-helix A domain; carbohydrate recognition domain; CRD domain;
KW treatment; angiogenesis; tumour; human.
XX
OS Homo sapiens.
XX
PN WO9931616-A1.
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PD 24-JUN-1999.
XX
PF 16-DEC-1998; 98WO-US026783.
XX
PR 16-DEC-1997; 97US-0069727P.
XX
PA (HARD) HARVARD COLLEGE.
XX
PI Olsen BR, Hohenester E, Timpl R, Sasaki T;
XX
DR WPI; 1999-395243/33.
DR N-PSDB; AAX78379.
XX
PT Identifying mimetics of mammalian endostatin.
XX
PS Disclosure; Fig 5A-C; 75pp; English.
XX
CC This invention describes a novel method for identifying mimetics of
CC mammalian endostatin. The method comprises identifying a compound having
CC atomic coordinates with non-trivial similarity to selected coordinates of
CC atoms of a mammalian endostatin involves (a) providing a library of
CC atomic coordinates of compounds in a library of candidate compounds, (b)
CC comparing the library of atomic coordinates to the selected coordinates
CC of a mammalian endostatin and (c) selecting from the library at least one
CC candidate compound on the basis of selection criteria which include
CC similarities between the atomic coordinates of the selected candidate
CC compound and the atomic coordinates of the mammalian endostatin. The
CC invention also describes the use of an anti-angiogenic fragment of
CC endostatin comprising a domain selected from a heparin binding domain, a
CC receptor binding domain, and exposed on alpha-helix A domain, and a
CC carbohydrate recognition domain (CRD) domain. The methods can be used for
CC designing and selecting endostatin mimics. The compounds identified can
CC be used for treating undesired angiogenesis, e.g. tumours. This sequence
CC represents human alpha1(XVIII) collagen which is used in the description
CC of the method
XX
SQ Sequence 684 AA;

Query Match 100.0%; Score 7; DB 2; Length 684;
Best Local Similarity 100.0%; Pred. No. 20;
Matches 7; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 QPGPPGP 7
              |||||||
Db        310 QPGPPGP 316
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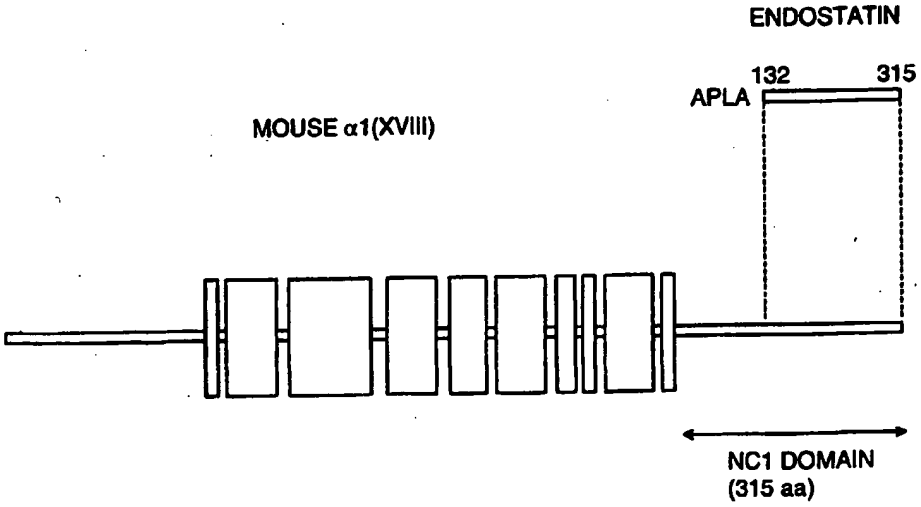

(57) Abstract

A detailed map of atomic coordinates of active mammalian endostatin is used in a computer–based method to identify mimics having endostatin coordinates. Based on the coordinates, the computer will identify compounds having atomic coordinates with non–trivial similarity to selected coordinates of atoms of a mammalian endostatin. The method includes: a) providing a library of atomic coordinates of compounds in a library of candidate compounds; b) comparing the library atomic coordinates to the selected coordinates of a mammalian endostatin; and c) selecting from the library at least one candidate compound on the basis of selection criteria which include similarities between the atomic coordinates of the selected candidate compound and the atomic coordinates of the mammalian endostatin.

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COMPUTER-GENERATED MIMETICS WITH ENDOSTATIN COORDINATES

Statement as to Federally Sponsored Research

This invention was supported in part by NIH grant AR36820, and the U.S. government has certain rights in the invention.

Field of the Invention

This invention is in the general field of computer-aided design or identification of organic compounds that mimic useful functions of known compounds.

Background of the Invention

Computers can be used to design or identify organic compounds that mimic the function(s) of known biological compounds. For example computers can be used to compare the atomic coordinates of key atoms of the known compounds to coordinates of atoms in known biological compounds.

Summary of the Invention

We have obtained a detailed map of atomic coordinates of active mammalian endostatin, and one prefered embodiment of the invention features computer generated mimics having endostatin coordinates. More generally, one aspect of the invention features a method of identifying a compound having atomic coordinates with non-trivial similarity to selected coordinates of atoms of a mammalian endostatin. The method includes: a) providing a library of atomic coordinates of compounds in a library of candidate compounds; b) comparing the library atomic coordinates to selected coordinates of a mammalian endostatin; and c) selecting from the library at least one candidate compound on the basis of selection criteria which include similarities between the atomic coordinates of the candidate compound and the selected atomic coordinates of a mammalian endostatin. We have identified certain key amino acid residues, and we predict that compounds (particularly non-peptides,

meaning compounds that are not readily subject to cleavage by enzymes that cleave naturally occuring peptide bonds) having atomic coordinates close to or identical to the coordinates of the atoms in those key endostatin residues will retain improtant endostatin function, particularly anti-angiogenic function. Some of the key epitopes (endostatin surface areas) containing those residues are: a heparin binding epitope, residues exposed α-helix A and a receptor or ligand binding epitope, which may involve an endostatin fold related to the CRD (E-selectin) oligosaccharide binding site. Other important epitopes may include those amino acids which are necessary for proteolytic cleavage. Preferably the endostatin coordinates used for selecting candidate molecules are from one or more of these surface areas (epitopes) in human endostatin. For human endostatin some of these residues are: a) Arg154, Arg157, Arg168, Arg177, Arg183, Arg192, Arg193, Arg 196, Arg258, Arg 259, and Arg 269; b) Phe161 and Phe164; and Glu266, Leu283, Ser291, His296, His297, and Tyr299. For mouse endostatin the corresponding residues are: a) Arg155, Arg158, Arg169, Arg178, Arg184, Arg 193, Arg 194, Arg197, Arg259, Arg270; b) Phe162 or Phe165; c) Glu267; Leu 284; Lys292; His297; Asn298; Tyr300. Numbering sequences given above correspond to position in NC1.

Typically the selected coordinates of endostatin atoms are stored in a computer-readable medium, and compared to coordinates of candidate compounds also stored in a computer-readable medium.

In other aspects, the invention includes anti-angiogenic fragments of endostatin comprising an epitope selected from the group consisting of a heparin binding epitope, a receptor binding epitope, an epitope exposed on α-helix, and an epitope from an endostatin fold related to the CRD (E-selectin) oligosaccharide binding

site. The invention further includes methods of treating undesired angiogenesis by administering to a patient an anti-angiogenic amount of such fragments or of a compound identified by the above method.

Brief Description of the Drawings

Fig. 1 depicts the domain structure of endostatin. Triple-helical domains are indicated by rectangular boxes; non-triple-helical regions are indicated by heavy lines. The region in the COOH-terminal NC1 domain that corresponds to the proteolytic fragment endostatin is indicated. The numbering scheme is based on position in the NC1 domain as described below. The recombinant endostatin used in this work contains an APLA sequence at the NH_2 terminus as a result of the cloning process, which is fortuitously identical to the α1(XVIII) collagen NC1 sequence at Leu-130 and Ala-131.

Fig. 2 shows electron density maps of endostatin in the region around the β strand P, with the disulfide bond between Cys-164 and Cys-304 in the center. In the upper panel is the MIRAS-phased map at 2.2Å resolution after density modification. In the lower panel is the final $2F_{obs}-F_{calc}$ map at 1.5Å resolution. Both maps are contoured at the 1.0σ level and are shown with the refined model superimposed. A modified version of MOLSCRIPT (Kraulis, 1991) was used.

Figs. 3A-3C show endostatin structure. Fig. 3A is a stereo C-atom trace. Spheres denote every tenth carbon atom and every 20th residue is labelled starting at Val-140. Disulfide bridges are shown with thick bands. Fig. 3B is a cartoon representation, with β strands sequentially labelled A through P. α helices are labeled. Disulfide bridges are also shown. Fig. 3C is a topology diagram. Heavy and thin diagonal lines indicate connections above and below the large β sheet,

respectively. Figs. 3A and 3B were made with MOLSCRIPT (Kraulis, 1991).

Figs. 4A and 4B are electrostatic surface representation of endostatin. Dark regions indicate positive potential, and light regions indicate negative potential. The NH_2 and the COOH termini are indicated. Basic residues and the solvent-exposed side chains of Phe-162 and Phe-165 are labeled. The hatched areas corresponds to the oligosaccharide binding site of C-type lectin CRDs. Fig. 5A and 5B are related by a rotation of 130° about the horizontal axis. The Figs. were made by GRASP (Nicholls, 1992).

Fig. 5 (PRIOR ART) shows the nucleotide sequence of cDNA and the inferred amino acid sequence of human α1(XVIII) collagen, compared to the amino acid sequence of mouse α1(XVIII). Only residues that are different between the human and mouse sequences are shown for the mouse. Gaps (-) or insertions (X) are shown. This figure is taken from FIG. 2 of Oh et al. *Genomics* 19:494-499 (1994).

Fig. 6 is a flow chart for performing computer-based compound selection.

Fig. 7 is a flow chart for computer-based compound design.

Description of the Preferred Embodiments

First we describe endostatin and therapies that can be developed using molecules which mimic endostatin's structure/function. Then we describe the process for designing and selecting endostatin mimics.

Endostatin

Endostatin is a known mammalian protein that inhibits angiogenesis, the process by which an adult mammal forms new blood vessels from existing vasculature by sprouting new capillaries. Angiogenesis is a complex

multi-stage process involving proteolytic degradation of the basement membrane, loss of endothelial cell adhesion, proliferation and migration of endothelial cells into the surrounding stroma, and finally re-adhesion of endothelial cells to form the lumen of the new capillary tube.

Ongoing angiogenesis is thought to be essential to support the rapid growth of solid tumors, and successful tumors may actively influence angiogenesis to sustain continuous cell proliferation. Their dependence on recruiting new blood vessels from the host makes tumors vulnerable to anti-angiogenic therapy. See Hannahan and Folkman (1996).

Some of the most potent angiogenic inhibitors are fragments derived from abundant extracellular proteins that themselves do not regulate angiogenesis. One such inhibitory fragment is a 20kDa COOH-terminal fragment of collagen XVIII. This heparin binding fragment termed endostatin specifically inhibits endothelial cell proliferation and potently inhibits angiogenesis and tumor growth. O'Reilly et al. (1997). Cycled therapy with recombinant endostatin reduced several experimental tumors, including Lewis lung carcinoma, to a dormant state and did not induce resistance. Dormancy persisted after a few cycles of treatment, even when therapy was discontinued. Boehm et al. (1997).

The α1(XVIII) collagen is an unusual collagen characterized by ten domains of triple-helical collagenous repeats separated by non-triple-helical repeats (Oh et al. 1994a; Rehn and Pihlajamiemi, 1994). It is expressed in a tissue-specific manner as three alternative splice variants and is localized mainly in perivascular basement membrane zones (Muragaki et al., 1995; Rehn and Pihlajaniemi, 1995). The last six of the triple-helical repeats of α1(XVIII) collagen are almost

identical in size to those of α1(XV) collagen (Myers et al., 1992), and the name multiplexins (for multiple triple helix domains and interruptions) has been coined for this new collagen family (Oh et al., 1994a). The α1(XVIII) collagen contains a non-collagenous COOH-terminal domain (NC1) of approximately 300 residues; the angiogenic inhibitor endostatin corresponds to the last 184 amino acid residues of the NC1 domain (Figure 1). Interestingly, this exactly matches the conserved region between the 1(XVIII) of α1(XV) COOH-terminal domains (Oh et al., 1994a).

We have solved the crystal structure of endostatin at 1.5 Å resolution, enabling careful selection of organic molecules that mimic endostatin's structure and function, and thereby can inhibit undesired angiogenesis, e.g. to control cancer. Without wishing to limit ourselves to a specific molecular mechanism, we note that a large basic surface area may be the heparin binding site of endostatin, and endostatin may exert its antiproliferative effect by competing with bFGF for binding to cell surface heparin sulfate proteoglycans, which could disrupt the mitogenic growth factor signal.

Protein Expression and Structure Determination

Endostatin was expressed at high levels as soluble protein in human embryonic kidney cells and was found to potently inhibit the bFGF-induced proliferation of endothelial cells, with IC_{50} of about 100 ng/ml (data not shown). The secreted protein spans the 184 COOH-terminal amino acid residues of mouse α1(XVIII) collagen and additionally contains the NH_2-terminal sequence APLA (Figure 1). To avoid ambiguities caused by the NH_2-terminal splicing of α1(XVIII) collagen (Muragaki et al., 1995; Rehn and Pihlajaniemi, 1995), we decided to number

the endostatin sequence relative to its position in the NC1 domain, starting at His-132.

The structure of endostatin was solved using crystals grown from ammonium phosphate at pH 5 Phases to 2.2 Å resolution were obtained by the multiple isomorphous replacement method and anomalous scattering (MIRAS) from three heavy atom derivatives (Table 1). The resulting electron density maps were of high quality (Figure 2A-2B), allowing the polypeptide chain to be traced without difficulty. The final structure, refined at 1.5 Å resolution, consists of residues Gln-138 to Phe-309 and a total of 83 water molecules. The first ten and last six residues are not visible and are presumed to be disordered.

Overall Structure

Endostatin folds into a single globular domain of approximate dimensions 35 Å x 30 Å x 30 Å (Figures 3A-3C). The structure is composed predominately of β sheet and loops, but also contains two α helices, one of them short. A total of 40% of the amino acid residues adopt an extended main chain conformation, but due to many irregularities, such as kinks and bulges, only 25% are actually contained in uninterrupted β strands spanning more than two residues. The fold of endostatin is intricate and is best described with reference to a schematic representation (Fig. 3C). The most prominent feature of the structure is a highly twisted mixed β sheet composed of sever strands (E,F,A,P,J,M,O). An α helix of 14 residues, α1, packs against one face of this sheet, whereas the other face is covered by elaborate loop structures involving a short stretch of antiparallel β sheet (extends G and N) and a second shorter α helix, α2. At the COOH terminus of strand A, the polypeptide chain bulges around a water molecule before re-establishing hydrogen bonding with the NH_2 terminus of

strand P for another two residues. The segment following α1 forms the short strand B, then kinks at Phe-180 and leads into the β hairpin C-D. Strands B, J and P form a triangular structure, at the center of which a water molecule hydrogen bonds with the peptide carbonyls of Phe-180 and Trp-251 and the amide nitrogen of Leu-303. This water molecule is deeply buried in the hydrophobic core and represents an integral part of the endostatin structure. Apart from the C-D β hairpin, there are two additional classical β hairpins, one extending the central β sheet at strand A (strands K and I), the other following strand J after a kink at Gly-253 (strands K and L). The overall arrangement of β strands in the endostatin structure can be described as a rather irregular β barrel propped open on one side by α2. Endostatin contains two disulfide bridges in a nested pattern, linking Cys-164 with Cys-304 and Cys-266 with Cys-296. The former disulfide bridge connects α1 to the central β sheet, and the latter circularizes a twisted loop containing strands M, N and O.

Despite the disjointed fold and the large fraction of irregular loop structures, endostatin is a compact molecule. All surface loops pack tightly against the body of the structure and many of them contribute to a large hydrophobic core. This core is divided into two regions of different size by strand J. The smaller core is centered around Trp-251 and is built up mainly from amino acid side chains contributed by strands J, M, O and P. A much more extensive hydrophobic core fills the large concave face of the central β sheet and this is also the region where most of the longer surface loops are found.

Strands A and P of endostatin are situated next to each other, engaged in antiparallel hydrogen bonding. As a result, the first and last residue defined by the

electron density (Gln-138 and Phe-309, respectively) are close in space. In the intact NC1 domain of collagen XVIII, endostatin is preceded by 131 residues. This NH_2-terminal portion of unknown structure is likely to interact with endostatin near Phe-309 and this interaction may well lead to an ordering of the C-terminus of endostatin, which significantly contains two large hydrophobic residues, Met-310 and Phe-313. We note that the side chains of Phe-162 and Phe-165, located next to each other on α1, are fully exposed to solvent (see Fig. 4A). In the crystal lattice they are covered by a hydrophobic packing contact, and we speculate that these two residues may be involved in interdomain interactions in the full length NC1 domain.

Collagen XVIII is a member of the so-called multiplexin family of collagens that also includes collagen XV. These two collagens are distinguished by COOH-terminal globular domains that share 58% sequence identity in their last 184 residues corresponding to endostatin in collagen XVIII (Oh et al., 1994a). We suggest that this common region represents a new extracellular module (Bork et al., 1996), as it appears unlikely that the compact endostatin structure is a soluble fragment excised from a larger domain. Interestingly, the ordered portion of the endostatin structure starts at an intro-exon boundary of α1(XVIII) collagen (Rehn et al., 1996). The autonomous folding of endostatin is also indicated by the high production rate of recombinant mouse endostatin (10-20 mg/l.d).

Comparison to Other Structures

An automated search of the DALI database (Holm and Sander, 1993; 1994) unexpectedly revealed that endostatin resembles the carbohydrate recognition domain (CRD) of mammalian C-type lectins (Weis et al., 1991; Drickamer, 1993). The highest scores (Z=3.1) were obtained with E-

selectin (Graves et al., 1994) and lithostatine, a homologue of the CRD that does not bind calcium or carbohydrate ligands (Bertrand et al., 1996). For the endostatin/E-selectin CRD pair, DALI identified 77 equivalent residues whose Cα atoms could be superimposed with an RMSD of 3.1 Å. The corresponding sequence identity of 9% is well below the threshold of statistical significance, but the high degree of structural similarity strongly argues for an evolutionary relationship. The entire β sheet structure of the E-selectin CRD is contained within the endostatin structure; only strands E and F of the central β sheet of topographically equivalent positions in the two proteins, but their disposition relative to the central β sheet varies. Significantly, both disulfide bridges in endostatin and E-selectin align almost perfectly when the three-dimensional structures are superimposed. Apart from Cys-296 and Cys-304, there are four additional amino acid residues in endostatin that have identical counterparts in the E-selectin structure. With the exception of the surface residue Gin-163 whose conservation may be adventitious, the location of these identities is telling: Pro-246 and Gyl-253 flank the crucial stand J in the large β sheet, and Trp-251 forms the nucleus of the smaller of the two hydrophobic cores in endostatin. The equivalent region in the C-type lectin CRD domain is the "WIGL" sequence (aromatic-aliphatic-glycine-aliphatic), which is the an important component of the C-type lectin consensus (Weis et al, 1991; Drickamer, 1993).

The difference between endostatin and the E-selectin CRD are concentrated in two regions, situated on opposite faces of the central β sheet. In E-selectin, the connection between α1 and strand β2 (the equivalent of endostatin βJ) is afforded by a short strand, helix α2,

an the loops preceding and following α2. The equivalent, much more elaborate region in endostatin contains eight, predominantly short stands (B to 1) as well as α2 and accounts for most of the extra residues of endostatin compared to E-selectin. In this region there is little similarity between the two structures, apart from the general location of α2. In E-selectin, β5 (the equivalent of endostatin βO) and the loop preceding β4 form a high affinity calcium binding site involved in oligosaccharide binding (Graves et al., 1994). There is no indication of calcium binding to endostatin and, indeed, we find that the long loop providing three of the five calcium ligands in E-selectin is shorter in endostatin and is arranged very differently, folded away from βO.

In summary, while endostatin is doubtless related to the C-type lectin CRD, it has lost one of the defining features of this protein family, namely calcium-dependent oligosaccharide binding. This is not an unprecedented observation. We have already mentioned lithostathine, a CRD homologue that acts as an inhibitor of stone formation in the pancreas (Bertrand et al., 1996). More relevantly, the recently elucidated structure of the Link module showed that this hyaluronan binding domain resembles the C-type lectin CRD but does not use calcium for glycosaminoglycan (GAG) binding (Kohda et al., 1996). This is further discussed below in conjunction with the ligand binding properties of endostatin.

A Putative Heparin Binding Site

The mechanism(s) by which endostatin inhibits endothelial cell proliferation and angiogenesis have yet to be defined. However, given the high affinity of endostatin for heparin, interference with the heparin sulfate requirement of bFGF signalling is one possibility. Endostatin contains a large number of basic residues. In particular arginines, and their

distribution on the protein surface provides a clue to the location of the heparin binding site. We note that of the 15 arginine residues present in mouse endostatin, all but one are fully conserved in the human protein, the exception being a conservative replacement by lysine (the overall identity between mouse and human endostatin is 87% (OH et al., 1994b). Given the genal location of arginines in surface loops, this high degree of conservation is noteworthy.

Falsam et al., 1996 shows two crystal structures of basic bFGF with bound heparin-derived tetra- and hexasaccharides. Basic residues may be crucial. These may be arranged as discrete clusters with a spacing that matches the distribution of GAG sulfate groups (Fromm et al., 1997). In addition, neutral polar residues may be required to provide hydrogen bonding partners for the sugar moieties (Thompson et al., 1994).

A representation of the surface electrostatic properties of endostatin is shown in Figs. 4A-4B. Eleven out of the total of 15 arginine residues cluster on one face of the molecule (Fig. 4A). This extensive basic patch (diameter = 20 Å) involves α1 and α2, strand B, the long loop connecting the C-D β hairpin to strand E, as well as strand L and the following loop around Cys-266. The solvent-exposed side chains of Phe-162 and Phe-165 (see above) are found at the periphery of the patch. A detailed inspection highlights one particular area as a candidate heparin binding site. The two arginine pairs Arg-193/Arg-194 and Arg-259/Arg-260 form the borders of a shallow depression, at the center of which the side chain of Tyr-215 emerges, surrounded by several additional polar residues. The residues forming this putative heparin binding site are contributed by the long irregular loop preceding strand E and strand L, both elements unique to endostatin when compared to the C-type

lectin CRD and the Link module. Binding of a larger GAG chain may involve additional arginines, possibly those centered around Arg-158.

Endostatin contains a second, less extensive basic patch roughly opposite the large area defined by the eleven arginines discussed above (Fig. 4B). This patch, composed mainly of residues contributed by the H-1 β hairpin and the NH_2 terminus of strand O, is of interest because it is close to the ligand binding site in the related C-type lectins CRD (Weis et al., 1992; Grave et al., 1994). While it is conceivable that heparin may also bind to this region, we note that some of the basic residues clearly serve structural purposes and would not be available for ligand binding (Arg-230,Arg-237, and Lys-248). Furthermore, our assignment of the heparin binding site to the face bearing exclusively arginine residues (Fig. 4A) is consistent with results from chemical modification, which demonstrate the involvement in heparin binding of several arginine but no lysine residues.

The Link module, a domain of approximately 100 residues found in several extracellular matrix proteins and in the cell surface receptor CD44, is a distant relative of the C-type lectin CRD that binds the GAG hyaluronan. In the TSG-6 Link module structure (Kohda et al., 1996), a critical basic residue in the loop preceding α1 and a patch of solvent-exposed aromatic side chains define a putative hyaluronan binding site, which partly overlaps with the surface area used by the CRDs for oligosaccharide binding. In endostatin the equivalent region involves mainly strands M and O and the connecting loop to strand P, which do not coincide with either of the two basic patches described above. We therefore believe that endostatin and the Link module employs partially distinct regions for GAG binding.

The function of the domain corresponding to endostatin in tissue-deposited collagen XVIII and XV is not known. Collagen XVIII is mainly found in vascular basement membrane regions (Muragaki et al., 1995), and the COOH-terminal NC1 domain may mediate interactions with basement membrane GAGs or proteoglycans. Full-length collagen XVIII is likely to be immobilized in some kind of network. Proteolytic cleavage in the NC1 domain, perhaps by a proteinase secreted by a tumor, could produce soluble endostatin, which would be free to diffuse to its targets and elicit its effects on endothelial cell proliferation and angiogenesis. The intact NC1 domain of collagen XVIII is not an inhibitor of angiogenesis (data not shown), corroborating earlier indications that the antiproliferative activity of endostatin may be cryptic (O'Reilly et al., 1997). It is not obvious from our structure how this regulation of activity may take place. Stearic blocking of an important epitope by the N-terminal portion of the NC1 domain is a possibility. However, other scenarios can be envisaged. For instance, the exposed and mobile polypeptide chain termini of endostatin may be important for the antiproliferative effect.

Key residues of endostatin can be delineated by site-directed mutagenesis. One function of interest is heparin binding. If endostatin acts by interfering with the heparan sulfate requirement of bFGF signalling, mutations which abolish endostatin-heparin binding would be expected to be accompanied by a loss of inhibition of endothelial cell proliferation and/or angiogenesis. A second site of interest may be a site which interacts with a protein or receptor, for example of the VEGF system, causing inhibition independent of GAG binding. Heparin binding may also turn out to be only one of several critical components of the mechanism, as is the

case with bFGF signalling. Finally, proteolytic unmasking of cryptic endostatin epitopes is a point of regulation.

Experimental procedures

Construction of Expression Vector

Mouse α1(XVIII) cDNA clone mc3b (Oh et al., 1994a) was used as a template to amplify the sequence encoding endostatin by polymerase chain reaction (PCR) with Vent polymerase (New England Biolabs) following the manufacturer's instructions. The primer for the 5' end was GTCAGCTAGCTCATACTCATCAGGAC and that for the 3' end was GTCACTCGAGCTATTTGGAGAAAGAGGTC. The primers contained in addition to the annealing sequences an NheI site at the 5' end or a stop codon followed by an XhoI site at the 3' end in order to allow the in-frame insertion of the construct into the BM-40 signal peptide (Mayer et al., 1993). The PcR fragment was cloned into the modified episomal expression vector pCEP-Pu (Kohfeldt et al., 1997). The sequence of the construct was confirmed by cycle sequencing using Dye Terminator Cycel Sequencing Ready Reaction Kit (ABI).

Expression and Purification of Recombinant Mouse Endostatin

Human embryonic kidney cells that express the EBNA-1 protein from Epstein-Barr virus (293-EBNA cells, Invitrogen) were used for transfection with the expression vector (Kohfeldt et al., 1997). Resistant cells were selected with puromycin (0.5 μg/ml) and used for collection of serum-free conditioned medium. The medium (=1 l) was dialyzed against 0.1 M NaCl, 0.05 M Tris-HCl (pH 7.4) and then applied onto a heparin-sepharose CL-6B column (2.5 x 20 cm, Pharmacia) equilibrated in the same buffer. A linear 0.1-1.0 M NaCl gradient (500 ml) was used for elution. Endostatin eluted at 0.4-0.5 M NaCl and was further purified on a

Superose 12 column (HR16/50, Pharmacia) equilibrated in 0.2 M ammonium acetate (pH 6.8). The purified product was soluble in neutral buffer and showed a single 22 kDa band in SDS gel electrophoresis under reducing conditions. The protein has a single NH_2-terminal sequence APLAHTHQ and contains less than one residue of hexosamine per molecule.

Crystallization and Data Collection

Crystals were obtained at room temperature by the hanging drop vapor diffusion method. Equal volumes (typically 2 μl) of a 10 mg/ml solution of endostatin in 5 mM Tris-HCl (pH 6.,8) and 1.5-1.7 M ammonium phosphate (pH 4.7-5.3) were mixed and equilibrated against 1 ml of the latter solution. The crystals belong to space group $P2_12_12_1$ with unit cell constants as = 45.6 Å, b = 54.0 Å, c = 65.9 Å. There is one molecule of endostatin in the asymmetric unit, resulting in a solvent content of 37%. For heavy atom soaks, crystals were stabilized in 1.8 M Li_2SO_4, 0.1 M Na-acetate (pH 5.3). All diffraction data except native II were collected at room temperature using a MAR image plate detector mounted on a rotating anode generator operated at 4 KW (CuKa radiation, λ = 1.54 Å). For derivative data collection, crystals were rotated around their carefully aligned a axis to minimize systematic errors in the measurement of Bijvoet pairs. Native II data were collected at room temperature on beamline 9.6 of the Daresbury Synchrotron Radiation Source (λ = 0.87 Å). Data were integrated with MOSFLM (Leslie, 1994) and reduced with programs of the CCP4 suite (Collaborative Computing Project No. 4, 1994). Data collection statistics are summarized in Table 1A.

Structure Solution and Refinement

Three heavy atom derivatives and the native 1 data were used for phasing by the MIRAS method (Table 1B). Soak conditions were 3 mM UO_2SO_4 for 3 days, 20 mM $K_2Pt(CN_4$

for 1 day, and 10 mM $NaAu(CN)_2$ for 2 days. Heavy atom sites were deduced from difference Patterson maps, brought to a common origin and hand by cross-phased difference Fourier maps, and refined with MLPHARE (Z. Otwinowski: Collaborative Computing project No. 4). Due to the high isomorphism of the U and Pt derivatives, useful MIRAS phases could be obtained to a resolution of 2.2 Å. The MIRAS map was subjected to density modification with DM (Cowtan and Main, 1996) in 'combine omit' mode employing solvent flattening, histogram matching and Sayre's equation. About 75% of the structure could be built with confidence into the resulting map using O (Jones et al., 1991). The remaining loop structures were added after combination of partial model phases with the experimental phases using SIGMAA (Read, 1986). The structure was first refined with X-PLOR (Brunger, 1992) against the native 1 data at 2.0 Å resolution to R_{cryst} = 0.192 (R_{free} = 0.237). Refinement against the synchrotron native II data was then initiated by a round of simulated annealing refinement starting from 3000 K to remove model bias, followed by conventional positional and B-factor refinement. The final model comprises residues 138 to 309 and 83 water molecules (Table 1C); 86.3% of the amino acid residues are in the most favorable regions of the Ramachandran plot, with the remaining 13.7% in additionally allowed regions, as defined by PROCHECK (Laskowski et al., 1993).

The coordinates and structural features of endostatin have been deposited in the Brookhaven Data Bank, and they are included as Appendix A to this patent application.

Methods of Designing Mimetics

Endostatin mimetics are compounds that perform a desired endostatin function, but which are not endostatin or peptide fragments of it. Mimetics may lack some or all of the endostatin L-amino acid linking peptide bonds that characterize most mammalian proteins and peptides. In this way, mimetics may avoid rapid degradation by peptide-cleaving enzymes, thereby enhancing their in vivo lifetime.

Preferred mimetics will retain a key endostatin function such as inhibition of endothelial cell proliferation. They will include atoms at positions similar to those of endostatin in the key eptipoes discussed above, including heparin binding, receptor binding, and epitopes controlling peptide cleavage from α1(XVIII) collagen.

The methods of the invention employ a computer-based methods for identifying compounds having a desired structure. More specifically, the invention uses the three-dimensional coordinates of a subset of the atoms in endostatin to determine peptide and non-peptide mimetic candidates by means of computer methods.

These computer-based methods fall into two broad classes: database methods and *de novo* design methods. In database methods the compound of interest is compared to all compounds present in a database of chemical structures and compounds whose structure is in some way similar to the compound of interest are identified. The structures in the database are based on either experimental data, generated by NMR or x-ray crystallography, or modeled three-dimensional structures based on two-dimensional (*i.e.*, sequence) data. In *de novo* design methods, models of compounds whose structure is in some way similar to the compound of interest are generated by a computer program using information derived

from known structure, *e.g.*, data generated by x-ray crystallography and/or theoretical rules. Such design methods can build a compound having a desired structure in either an atom-by-atom manner or by assembling stored small molecular fragments.

The success of both database and *de novo* method in identifying compounds with activities similar to the compound of interest depends on the identification of the functionally relevant portion of the compound of interest. For drugs, the functionally relevant portion is referred to a pharmacophore. A pharmacophore then is an arrangement of structural features and functional groups important for biological activity, *e.g.*, endostatin activity.

Not all identified compounds having the desired pharmacophore will act as an endostatin mimetic. The actual activity can be finally determined only by measuring the activity of the compound in relevant biological assays. However, the methods of the invention are extremely valuable because they can be used to greatly reduce the number of compounds which must be tested to identify an actual mimetic.

Programs suitable for generating predicted three-dimensional structures from two-dimensional data include: Concord (Tripos Associated, St. Louis, MO), 3-D Builder (Chemical Design Ltd., Oxford, U.K.), Catalyst (Bio-CAD Corp., Mountain View, CA), and Daylight (Abbott Laboratories, Abbott Park, IL).

Programs suitable for searching three-dimensional databases to identify molecules bearing a desired pharmacophore include: MACCS-3D and ISIS/3D (Molecular Design Ltd., San Leandro, CA), ChemDBS-3D (Chemical Design Ltd., Oxford, U.K.), and Sybyl/3DB Unity (Tripos Associates, St. Louis, MO).

Programs suitable for pharmacophore selection and design include: DISCO (Abbott Laboratories, Abbott Park, IL), Catalyst (Bio-CAD Corp., Mountain View, CA), and ChemDBS-3D (Chemical Design Ltd., Oxford, U.K.).

Databases of chemical structures are available from Cambridge Crystallographic Data Center (Cambridge, U.K.) and Chemical Abstracts Service (Columbus, OH).

De novo design programs include Ludi (Biosym Technologies Inc., San Diego, CA) and Aladdin (Daylight Chemical Information Systems, Irvine CA).

Those skilled in the art will recognize that the design of mimetic may require slight structural alteration or adjustment of a chemical structure designed or identified using the methods of the invention.

In general, chemical compounds identified or designed using the methods of the invention can be synthesized chemically and then tested for endostatin activity using any of the methods described below. The methods of the invention are particularly useful because they can be used to greatly decrease the number potential mimetics which must be screened for endostatin activity.

The invention may be implemented in hardware or software, or a combination of both. However, preferably, the invention is implemented in computer programs executing on programmable computers each comprising a processor, a data storage system including volatile and non-volatile memory and/or storage elements), at least one input device, and at least one output device. Program code is applied to input data to perform the functions described above and generate output information. The output information is applied to one or more output devices, in known fashion. The computer may be, for example, a personal computer, microcomputer, or work station of conventional design.

Each program is preferably implemented in a high level procedural or object oriented programming language to communicate with a computer system. However, the programs can be implemented in assembly or machine language, if desired. In any case, the language may be a compiled or interpreted language.

Each such computer program is preferably stored on a storage media or device (*e.g.*, ROM or magnetic diskette) readable by a general or special purpose programmable computer, for configuring and operating the computer when the storage media or device is read by the computer to perform the procedures described herein. The inventive system may also be considered to be implemented as a computer-readable storage medium, configured with a computer program, where the storage medium so configured causes a computer to operate in a specific and predefined manner to perform the functions described herein.

Fig. 6 is a flow chart showing a first method for identifying potential mimetics using a computer system. The method uses a programmed computer comprising a processor, a data storage system, at least one input device, and at least one output device, and comprises the steps of:

(1) inputting into the programmed computer through an input device data comprising the three-dimensional coordinates of a subset of the atoms in endostatin, thereby generating a criteria data set (STEP 100);

(2) comparing, using the processor, the criteria data set to a computer database of chemical structures stored in the computer data storage system (STEP 102);

(3) selecting from the database, using a program suitable for searching three-dimensional databases to identify molecules bearing a desired

pharmacophore (such as those described above or equivalents), chemical structures having a portion that is structurally similar to the criteria data set (STEP 104);

(4) outputting to an output device the selected chemical structures having a portion similar to the criteria data set (STEP 106).

Fig. 7 is a flow chart showing a second method for identifying potential mimetics of endostatin using a computer system. The method uses a programmed computer comprising a processor, a data storage system, at least one input device, and at least one output device, and comprises the steps of:

(1) inputting into the programmed computer through an input device data comprising the three-dimensional coordinates of a atoms of endostatin, thereby generating a criteria data set (STEP 200);

(2) constructing, using a program suitable for generating chemical structure models (such as those described above or equivalents), a model of a chemical structure having a portion that is structurally similar to the criteria data set (STEP 202);

(3) outputting to the output device the constructed model (STEP 204).

Confirmation of Biological Activity

In order to determine whether a molecule identified using the methods of the invention can act as an endostatin mimetic, one or more *in vitro* or *in vivo* assays of endostatin activity should be performed. For example, mimetic molecules should be able to inhibit endothelial cell proliferation in the following assay using human imbilical vein endothelial cells (HUVEC's) or human arterila endothelial cells (HAEC's).

Gelatin-coated multi-well plates are prepared by incubating 0.3ml of attachment factor solution (Cascade Biologic, Inc., Portland OR) for 30 min. at 37°C or for 2 hrs. at room temperature. The attachment factor solution is aspirated. A suspension of $2.5x10^4$ cells/ml of HUVEC in M200 (Cascade Biologic) supplemented with Low Serum Growth Supplement (LSGS, also from Cascade Biologic) is prepared. 0.5ml of the suspension is added to each well, and the cells are incubated at 37°C and 5%CO_2 for 24hrs.

The medium is then replaced with sample test solutions (e.g., with concentrations ranging from 0-500ng/ml) prepared from sample stock solutions by dilution with M200 supplemented with LSGS. 0.5ml of sample test solution is added to each well and incubated at 37°C and 5%CO_2 for 48hrs.

An MMT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrasolium bromide) assay is performed to determine cell proliferation. MMT is dissolved to 5mg/ml in PBS and filtered (0.2μm). 50μl of MMT solution is added to each well for the last 4 hours of the 48hr incubation. Medium is aspirated. 0.4ml of isopropanol with 0.04N HCl is added to each well and absorbance is measured at 570nm. Decreased absorbance relative to control indicates inhibition of proliferation.

Using assays based on the above procedures, we have determined that several endostatin-containing fragments inhibit endothelial cell proliferation at a level comparable to human endostatin. For example, human NC1-N-terminal segment, human NC1-C-terminal segment, and mouse endostatin fragments inhibit endothelial cell proliferation.

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PROVISIONAL APPLICATION

UNDER 37 CFR 1.53(b)(2)

APPENDIX A

TITLE: COMPUTER-GENERATED MIMETICS WITH ENDOSTATIN COORDINATES

APPLICANT: BJORN R. OLSEN
ERHARD HOHENESTER
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TAKAKO SASAKI

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REMA
REMA   crystal structure of mouse endostatin at 1.5 A resolution
REMA   authors: E Hohenester, T Sasaki, BR Olsen, and R Timpl
REMA
CRYST1  45.560  53.950  65.850 90.00 90.00 90.00
ATOM    1 CB  GLN  138     16.060 38.907 58.366 1.00 10.71
ATOM    2 CG  GLN  138     15.910 39.108 56.861 1.00 11.99
ATOM    3 CD  GLN  138     14.462 39.216 56.438 1.00 17.23
ATOM    4 OE1 GLN  138     13.740 40.078 56.909 1.00 19.56
ATOM    5 NE2 GLN  138     14.020 38.315 55.565 1.00 19.22
ATOM    6 C   GLN  138     16.020 36.457 58.023 1.00 16.16
ATOM    7 O   GLN  138     17.226 36.330 57.871 1.00 16.26
ATOM    8 N   GLN  138     15.825 37.355 60.311 1.00 19.63
ATOM    9 CA  GLN  138     15.467 37.593 58.873 1.00 15.07
ATOM   10 N   PRO  139     15.146 35.591 57.498 1.00 15.25
ATOM   11 CD  PRO  139     13.687 35.481 57.641 1.00 15.29
ATOM   12 CA  PRO  139     15.679 34.496 56.678 1.00 12.81
ATOM   13 CB  PRO  139     14.453 33.619 56.444 1.00 13.97
ATOM   14 CG  PRO  139     13.327 34.567 56.473 1.00 19.89
ATOM   15 C   PRO  139     16.271 34.987 55.379 1.00  9.18
ATOM   16 O   PRO  139     15.816 35.984 54.818 1.00 11.04
ATOM   17 N   VAL  140     17.301 34.287 54.921 1.00 10.21
ATOM   18 CA  VAL  140     17.960 34.598 53.657 1.00  9.99
ATOM   19 CB  VAL  140     19.204 35.503 53.854 1.00 10.45
ATOM   20 CG1 VAL  140     18.813 36.882 54.376 1.00 10.92
ATOM   21 CG2 VAL  140     20.197 34.833 54.753 1.00  9.04
ATOM   22 C   VAL  140     18.458 33.277 53.077 1.00 11.74
ATOM   23 O   VAL  140     18.630 32.309 53.809 1.00 13.00
ATOM   24 N   LEU  141     18.697 33.256 51.768 1.00 10.15
ATOM   25 CA  LEU  141     19.251 32.096 51.073 1.00  9.08
ATOM   26 CB  LEU  141     18.272 31.542 50.033 1.00 10.41
ATOM   27 CG  LEU  141     16.952 30.968 50.545 1.00 12.91
ATOM   28 CD1 LEU  141     16.125 30.494 49.349 1.00 13.77
ATOM   29 CD2 LEU  141     17.215 29.825 51.518 1.00 10.92
ATOM   30 C   LEU  141     20.495 32.597 50.355 1.00  8.62
ATOM   31 O   LEU  141     20.434 33.581 49.600 1.00  9.84
ATOM   32 N   HIS  142     21.622 31.931 50.575 1.00  6.26
ATOM   33 CA  HIS  142     22.871 32.331 49.933 1.00  7.37
ATOM   34 CB  HIS  142     24.070 31.977 50.812 1.00  6.13
ATOM   35 CG  HIS  142     24.093 32.703 52.125 1.00  9.30
ATOM   36 CD2 HIS  142     24.697 33.863 52.491 1.00 11.21
ATOM   37 ND1 HIS  142     23.408 32.261 53.232 1.00 10.67
ATOM   38 CE1 HIS  142     23.583 33.115 54.229 1.00 11.23
ATOM   39 NE2 HIS  142     24.360 34.089 53.807 1.00  9.19
ATOM   40 C   HIS  142     23.078 31.728 48.521 1.00  9.63
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ATOM 41 O HIS 142 22.824 30.530 48.298 1.00 8.50
ATOM 42 N LEU 143 23.531 32.561 47.587 1.00 5.90
ATOM 43 CA LEU 143 23.840 32.138 46.217 1.00 6.16
ATOM 44 CB LEU 143 23.086 32.994 45.199 1.00 7.80
ATOM 45 CG LEU 143 23.227 32.617 43.721 1.00 8.59
ATOM 46 CD1 LEU 143 22.603 31.276 43.438 1.00 8.94
ATOM 47 CD2 LEU 143 22.540 33.694 42.866 1.00 11.98
ATOM 48 C LEU 143 25.355 32.363 46.123 1.00 8.08
ATOM 49 O LEU 143 25.829 33.492 46.235 1.00 8.41
ATOM 50 N VAL 144 26.116 31.289 45.927 1.00 7.00
ATOM 51 CA VAL 144 27.570 31.337 45.956 1.00 6.28
ATOM 52 CB VAL 144 28.077 30.721 47.303 1.00 7.09
ATOM 53 CG1 VAL 144 29.576 30.910 47.456 1.00 9.37
ATOM 54 CG2 VAL 144 27.352 31.358 48.494 1.00 10.88
ATOM 55 C VAL 144 28.175 30.546 44.806 1.00 7.86
ATOM 56 O VAL 144 27.695 29.470 44.461 1.00 8.99
ATOM 57 N ALA 145 29.231 31.075 44.207 1.00 7.05
ATOM 58 CA ALA 145 29.870 30.388 43.092 1.00 8.14
ATOM 59 CB ALA 145 30.501 31.423 42.154 1.00 8.87
ATOM 60 C ALA 145 30.938 29.359 43.511 1.00 8.47
ATOM 61 O ALA 145 31.633 29.530 44.538 1.00 8.37
ATOM 62 N LEU 146 31.071 28.302 42.709 1.00 7.30
ATOM 63 CA LEU 146 32.131 27.326 42.934 1.00 8.01
ATOM 64 CB LEU 146 32.013 26.134 41.982 1.00 6.67
ATOM 65 CG LEU 146 30.862 25.161 42.280 1.00 9.61
ATOM 66 CD1 LEU 146 30.912 24.036 41.268 1.00 9.50
ATOM 67 CD2 LEU 146 31.010 24.558 43.693 1.00 11.47
ATOM 68 C LEU 146 33.478 28.051 42.732 1.00 7.11
ATOM 69 O LEU 146 33.572 29.018 41.964 1.00 9.42
ATOM 70 N ASN 147 34.523 27.552 43.376 1.00 6.40
ATOM 71 CA ASN 147 35.832 28.192 43.333 1.00 7.10
ATOM 72 CB ASN 147 36.705 27.692 44.489 1.00 7.91
ATOM 73 CG ASN 147 36.176 28.129 45.853 1.00 8.97
ATOM 74 OD1 ASN 147 35.563 29.189 45.993 1.00 11.21
ATOM 75 ND2 ASN 147 36.423 27.309 46.870 1.00 10.82
ATOM 76 C ASN 147 36.591 28.134 42.011 1.00 9.58
ATOM 77 O ASN 147 37.658 28.738 41.896 1.00 10.63
ATOM 78 N THR 148 36.098 27.348 41.058 1.00 7.40
ATOM 79 CA THR 148 36.722 27.297 39.738 1.00 9.45
ATOM 80 CB THR 148 37.623 26.049 39.514 1.00 13.02
ATOM 81 OG1 THR 148 36.799 24.881 39.398 1.00 17.83
ATOM 82 CG2 THR 148 38.619 25.862 40.643 1.00 15.46
ATOM 83 C THR 148 35.616 27.168 38.713 1.00 9.36
ATOM 84 O THR 148 34.503 26.758 39.042 1.00 8.96
ATOM 85 N PRO 149 35.877 27.637 37.473 1.00 12.03
ATOM 86 CD PRO 149 37.022 28.417 36.982 1.00 16.15
ATOM 87 CA PRO 149 34.849 27.500 36.441 1.00 10.16
ATOM 88 CB PRO 149 35.412 28.335 35.287 1.00 12.46
ATOM 89 CG PRO 149 36.883 28.269 35.478 1.00 15.97
ATOM 90 C PRO 149 34.840 26.015 36.092 1.00 9.92
ATOM 91 O PRO 149 35.786 25.280 36.438 1.00 12.33
ATOM 92 N LEU 150 33.777 25.569 35.431 1.00 9.68
ATOM 93 CA LEU 150 33.653 24.181 35.020 1.00 8.42

ATOM 94 CB LEU 150 32.665 23.451 35.933 1.00 11.10
ATOM 95 CG LEU 150 33.047 23.170 37.403 1.00 13.54
ATOM 96 CD1 LEU 150 31.913 22.375 38.058 1.00 15.50
ATOM 97 CD2 LEU 150 34.336 22.387 37.477 1.00 14.35
ATOM 98 C LEU 150 33.114 24.130 33.610 1.00 7.98
ATOM 99 O LEU 150 32.371 25.015 33.190 1.00 8.15
ATOM 100 N SER 151 33.521 23.116 32.862 1.00 9.42
ATOM 101 CA SER 151 32.987 22.923 31.515 1.00 9.11
ATOM 102 CB SER 151 33.938 22.048 30.692 1.00 10.20
ATOM 103 OG SER 151 33.940 20.711 31.169 1.00 10.67
ATOM 104 C SER 151 31.657 22.175 31.729 1.00 9.32
ATOM 105 O SER 151 31.269 21.901 32.866 1.00 10.06
ATOM 106 N GLY 152 30.984 21.809 30.644 1.00 7.94
ATOM 107 CA GLY 152 29.736 21.087 30.761 1.00 8.69
ATOM 108 C GLY 152 29.902 19.660 31.274 1.00 9.35
ATOM 109 O GLY 152 28.917 19.036 31.659 1.00 11.59
ATOM 110 N GLY 153 31.126 19.127 31.230 1.00 8.17
ATOM 111 CA GLY 153 31.381 17.774 31.719 1.00 10.98
ATOM 112 C GLY 153 31.692 17.856 33.202 1.00 10.16
ATOM 113 O GLY 153 32.860 17.943 33.591 1.00 11.38
ATOM 114 N MET 154 30.642 17.821 34.027 1.00 10.00
ATOM 115 CA MET 154 30.768 17.957 35.488 1.00 9.58
ATOM 116 CB MET 154 29.716 18.945 35.997 1.00 9.96
ATOM 117 CG MET 154 29.738 20.301 35.324 1.00 12.59
ATOM 118 SD MET 154 28.413 21.305 35.982 1.00 14.27
ATOM 119 CE MET 154 28.373 22.677 34.791 1.00 16.15
ATOM 120 C MET 154 30.553 16.668 36.256 1.00 11.76
ATOM 121 O MET 154 30.429 16.701 37.484 1.00 9.48
ATOM 122 N ARG 155 30.520 15.551 35.531 1.00 12.28
ATOM 123 CA ARG 155 30.250 14.226 36.102 1.00 11.91
ATOM 124 CB ARG 155 31.163 13.908 37.289 1.00 11.17
ATOM 125 CG ARG 155 32.637 13.800 36.905 1.00 17.34
ATOM 126 CD ARG 155 33.464 13.057 37.966 1.00 21.82
ATOM 127 NE ARG 155 33.823 13.921 39.084 1.00 36.87
ATOM 128 CZ ARG 155 34.692 14.924 39.004 0.00 30.58
ATOM 129 NH1 ARG 155 35.307 15.197 37.854 0.00 29.77
ATOM 130 NH2 ARG 155 34.911 15.687 40.066 0.00 29.77
ATOM 131 C ARG 155 28.784 14.188 36.516 1.00 12.08
ATOM 132 O ARG 155 28.404 13.550 37.513 1.00 12.85
ATOM 133 N GLY 156 27.958 14.870 35.725 1.00 8.74
ATOM 134 CA GLY 156 26.539 14.929 35.972 1.00 7.52
ATOM 135 C GLY 156 26.163 15.848 37.120 1.00 7.97
ATOM 136 O GLY 156 27.025 16.469 37.746 1.00 8.74
ATOM 137 N ILE 157 24.868 15.894 37.421 1.00 9.58
ATOM 138 CA ILE 157 24.382 16.725 38.498 1.00 8.21
ATOM 139 CB ILE 157 22.849 16.831 38.459 1.00 12.87
ATOM 140 CG2 ILE 157 22.212 15.495 38.838 1.00 14.12
ATOM 141 CG1 ILE 157 22.388 17.998 39.353 1.00 13.81
ATOM 142 CD1 ILE 157 22.782 19.366 38.796 1.00 13.09
ATOM 143 C ILE 157 24.906 16.218 39.862 1.00 8.75
ATOM 144 O ILE 157 25.107 17.011 40.771 1.00 7.94
ATOM 145 N ARG 158 25.123 14.905 40.011 1.00 8.52
ATOM 146 CA ARG 158 25.670 14.382 41.272 1.00 8.29

ATOM 147 CB ARG 158 25.735 12.841 41.263 1.00 9.85
ATOM 148 CG ARG 158 24.374 12.165 41.245 1.00 13.49
ATOM 149 CD ARG 158 24.497 10.663 41.084 1.00 12.24
ATOM 150 NE ARG 158 23.220 10.010 41.373 1.00 15.33
ATOM 151 CZ ARG 158 22.969 8.710 41.187 1.00 15.84
ATOM 152 NH1 ARG 158 23.917 7.910 40.708 1.00 14.08
ATOM 153 NH2 ARG 158 21.770 8.214 41.490 1.00 17.98
ATOM 154 C ARG 158 27.075 14.973 41.488 1.00 8.10
ATOM 155 O ARG 158 27.445 15.301 42.616 1.00 10.27
ATOM 156 N GLY 159 27.832 15.147 40.397 1.00 8.31
ATOM 157 CA GLY 159 29.172 15.709 40.472 1.00 7.59
ATOM 158 C GLY 159 29.130 17.171 40.900 1.00 10.13
ATOM 159 O GLY 159 29.836 17.592 41.819 1.00 9.79
ATOM 160 N ALA 160 28.276 17.946 40.240 1.00 9.09
ATOM 161 CA ALA 160 28.119 19.371 40.547 1.00 8.50
ATOM 162 CB ALA 160 27.173 20.028 39.550 1.00 10.08
ATOM 163 C ALA 160 27.606 19.567 41.976 1.00 7.04
ATOM 164 O ALA 160 28.133 20.388 42.727 1.00 8.57
ATOM 165 N ASP 161 26.583 18.812 42.352 1.00 6.23
ATOM 166 CA ASP 161 26.034 18.902 43.708 1.00 6.78
ATOM 167 CB ASP 161 24.830 17.955 43.883 1.00 9.35
ATOM 168 CG ASP 161 23.504 18.553 43.386 1.00 11.70
ATOM 169 OD1 ASP 161 23.458 19.756 43.070 1.00 9.81
ATOM 170 OD2 ASP 161 22.484 17.814 43.340 1.00 11.63
ATOM 171 C ASP 161 27.092 18.546 44.752 1.00 7.76
ATOM 172 O ASP 161 27.152 19.161 45.818 1.00 8.73
ATOM 173 N PHE 162 27.939 17.558 44.459 1.00 7.42
ATOM 174 CA PHE 162 28.979 17.169 45.409 1.00 6.73
ATOM 175 CB PHE 162 29.656 15.869 44.963 1.00 7.02
ATOM 176 CG PHE 162 30.679 15.369 45.929 1.00 9.17
ATOM 177 CD1 PHE 162 30.384 15.275 47.285 1.00 11.91
ATOM 178 CD2 PHE 162 31.931 14.981 45.490 1.00 17.16
ATOM 179 CE1 PHE 162 31.340 14.787 48.203 1.00 16.73
ATOM 180 CE2 PHE 162 32.888 14.495 46.391 1.00 22.21
ATOM 181 CZ PHE 162 32.591 14.399 47.746 1.00 14.81
ATOM 182 C PHE 162 30.014 18.309 45.573 1.00 9.46
ATOM 183 O PHE 162 30.534 18.548 46.671 1.00 9.44
ATOM 184 N GLN 163 30.336 19.000 44.477 1.00 8.27
ATOM 185 CA GLN 163 31.272 20.124 44.549 1.00 7.65
ATOM 186 CB GLN 163 31.576 20.667 43.151 1.00 9.20
ATOM 187 CG GLN 163 32.539 19.790 42.365 1.00 18.91
ATOM 188 CD GLN 163 33.857 19.587 43.107 1.00 39.76
ATOM 189 OE1 GLN 163 34.541 20.556 43.459 1.00 52.67
ATOM 190 NE2 GLN 163 34.201 18.326 43.385 1.00 48.77
ATOM 191 C GLN 163 30.694 21.215 45.464 1.00 7.86
ATOM 192 O GLN 163 31.414 21.754 46.307 1.00 9.18
ATOM 193 N CYS 164 29.409 21.535 45.295 1.00 5.94
ATOM 194 CA CYS 164 28.751 22.532 46.142 1.00 5.67
ATOM 195 C CYS 164 28.836 22.113 47.619 1.00 8.49
ATOM 196 O CYS 164 29.109 22.938 48.498 1.00 11.21
ATOM 197 CB CYS 164 27.283 22.704 45.742 1.00 7.87
ATOM 198 SG CYS 164 27.037 23.568 44.153 1.00 8.48
ATOM 199 N PHE 165 28.589 20.834 47.880 1.00 8.20

ATOM 200 CA PHE 165 28.648 20.279 49.237 1.00 9.36
ATOM 201 CB PHE 165 28.264 18.786 49.206 1.00 7.82
ATOM 202 CG PHE 165 28.450 18.079 50.530 1.00 7.97
ATOM 203 CD1 PHE 165 27.409 18.024 51.458 1.00 12.10
ATOM 204 CD2 PHE 165 29.665 17.482 50.851 1.00 14.48
ATOM 205 CE1 PHE 165 27.587 17.380 52.699 1.00 12.63
ATOM 206 CE2 PHE 165 29.847 16.842 52.084 1.00 17.07
ATOM 207 CZ PHE 165 28.806 16.798 52.997 1.00 10.01
ATOM 208 C PHE 165 30.052 20.435 49.828 1.00 9.82
ATOM 209 O PHE 165 30.228 20.953 50.939 1.00 7.80
ATOM 210 N GLN 166 31.056 19.987 49.079 1.00 7.84
ATOM 211 CA GLN 166 32.436 20.052 49.536 1.00 9.67
ATOM 212 CB GLN 166 33.367 19.386 48.523 1.00 10.91
ATOM 213 CG GLN 166 33.330 17.887 48.588 1.00 18.10
ATOM 214 CD GLN 166 33.824 17.357 49.945 1.00 34.87
ATOM 215 OE1 GLN 166 34.965 16.907 50.058 1.00 42.81
ATOM 216 NE2 GLN 166 32.972 17.419 50.974 1.00 32.60
ATOM 217 C GLN 166 32.928 21.468 49.803 1.00 11.38
ATOM 218 O GLN 166 33.501 21.756 50.868 1.00 11.23
ATOM 219 N GLN 167 32.670 22.368 48.862 1.00 9.13
ATOM 220 CA GLN 167 33.154 23.727 49.007 1.00 8.13
ATOM 221 CB GLN 167 33.158 24.409 47.651 1.00 8.05
ATOM 222 CG GLN 167 34.112 23.695 46.726 1.00 11.07
ATOM 223 CD GLN 167 34.234 24.338 45.357 1.00 12.90
ATOM 224 OE1 GLN 167 33.986 25.533 45.199 1.00 10.57
ATOM 225 NE2 GLN 167 34.645 23.552 44.364 1.00 12.82
ATOM 226 C GLN 167 32.479 24.543 50.094 1.00 8.77
ATOM 227 O GLN 167 33.132 25.365 50.754 1.00 9.77
ATOM 228 N ALA 168 31.202 24.274 50.335 1.00 7.44
ATOM 229 CA ALA 168 30.475 24.976 51.404 1.00 8.42
ATOM 230 CB ALA 168 28.964 24.700 51.304 1.00 9.12
ATOM 231 C ALA 168 31.010 24.509 52.773 1.00 9.57
ATOM 232 O ALA 168 31.233 25.310 53.683 1.00 11.46
ATOM 233 N ARG 169 31.219 23.203 52.890 1.00 9.90
ATOM 234 CA ARG 169 31.711 22.578 54.106 1.00 11.80
ATOM 235 CB ARG 169 31.753 21.064 53.880 1.00 15.49
ATOM 236 CG ARG 169 32.049 20.219 55.079 1.00 37.27
ATOM 237 CD ARG 169 32.180 18.759 54.671 1.00 52.08
ATOM 238 NE ARG 169 31.918 17.856 55.791 1.00 65.31
ATOM 239 CZ ARG 169 30.697 17.580 56.255 1.00 73.82
ATOM 240 NH1 ARG 169 29.625 18.141 55.690 1.00 74.58
ATOM 241 NH2 ARG 169 30.543 16.755 57.292 1.00 77.05
ATOM 242 C ARG 169 33.107 23.096 54.457 1.00 12.57
ATOM 243 O ARG 169 33.404 23.346 55.629 1.00 12.02
ATOM 244 N ALA 170 33.943 23.291 53.437 1.00 10.85
ATOM 245 CA ALA 170 35.316 23.755 53.619 1.00 10.67
ATOM 246 CB ALA 170 36.058 23.765 52.286 1.00 8.66
ATOM 247 C ALA 170 35.392 25.132 54.264 1.00 11.92
ATOM 248 O ALA 170 36.365 25.441 54.943 1.00 14.09
ATOM 249 N VAL 171 34.375 25.964 54.046 1.00 10.84
ATOM 250 CA VAL 171 34.365 27.308 54.621 1.00 10.43
ATOM 251 CB VAL 171 34.126 28.399 53.543 1.00 11.31
ATOM 252 CG1 VAL 171 35.245 28.335 52.525 1.00 14.10

ATOM 253 CG2 VAL 171 32.773 28.225 52.852 1.00 11.12
ATOM 254 C VAL 171 33.424 27.471 55.797 1.00 10.80
ATOM 255 O VAL 171 33.055 28.579 56.167 1.00 12.10
ATOM 256 N GLY 172 32.977 26.356 56.340 1.00 12.04
ATOM 257 CA GLY 172 32.131 26.429 57.511 1.00 13.35
ATOM 258 C GLY 172 30.699 26.875 57.342 1.00 15.12
ATOM 259 O GLY 172 30.073 27.285 58.318 1.00 15.40
ATOM 260 N LEU 173 30.168 26.818 56.125 1.00 13.41
ATOM 261 CA LEU 173 28.768 27.183 55.909 1.00 15.44
ATOM 262 CB LEU 173 28.519 27.534 54.455 1.00 14.81
ATOM 263 CG LEU 173 29.272 28.782 53.997 1.00 19.11
ATOM 264 CD1 LEU 173 28.947 29.080 52.537 1.00 20.09
ATOM 265 CD2 LEU 173 28.899 29.978 54.883 1.00 24.38
ATOM 266 C LEU 173 27.925 25.985 56.307 1.00 21.13
ATOM 267 O LEU 173 28.253 24.851 55.961 1.00 24.24
ATOM 268 N SER 174 26.839 26.231 57.033 1.00 26.10
ATOM 269 CA SER 174 25.980 25.152 57.527 1.00 28.96
ATOM 270 CB SER 174 25.478 25.501 58.935 1.00 34.55
ATOM 271 OG SER 174 26.566 25.731 59.820 1.00 47.56
ATOM 272 C SER 174 24.793 24.721 56.667 1.00 28.64
ATOM 273 O SER 174 24.275 23.611 56.833 1.00 33.02
ATOM 274 N GLY 175 24.331 25.593 55.785 1.00 21.73
ATOM 275 CA GLY 175 23.188 25.223 54.975 1.00 23.45
ATOM 276 C GLY 175 23.441 24.121 53.963 1.00 22.56
ATOM 277 O GLY 175 24.584 23.685 53.761 1.00 23.28
ATOM 278 N THR 176 22.360 23.691 53.315 1.00 19.93
ATOM 279 CA THR 176 22.409 22.665 52.280 1.00 18.67
ATOM 280 CB THR 176 21.163 21.749 52.340 1.00 27.39
ATOM 281 OG1 THR 176 21.035 21.204 53.665 1.00 33.04
ATOM 282 CG2 THR 176 21.293 20.599 51.329 1.00 29.21
ATOM 283 C THR 176 22.468 23.362 50.914 1.00 13.33
ATOM 284 O THR 176 21.508 23.988 50.481 1.00 15.59
ATOM 285 N PHE 177 23.611 23.254 50.254 1.00 11.56
ATOM 286 CA PHE 177 23.816 23.881 48.954 1.00 10.99
ATOM 287 CB PHE 177 25.181 24.551 48.911 1.00 9.82
ATOM 288 CG PHE 177 25.273 25.774 49.774 1.00 13.27
ATOM 289 CD1 PHE 177 25.489 25.656 51.147 1.00 11.48
ATOM 290 CD2 PHE 177 25.140 27.042 49.218 1.00 11.67
ATOM 291 CE1 PHE 177 25.572 26.782 51.948 1.00 13.02
ATOM 292 CE2 PHE 177 25.226 28.170 50.021 1.00 15.24
ATOM 293 CZ PHE 177 25.442 28.037 51.386 1.00 12.92
ATOM 294 C PHE 177 23.727 22.897 47.811 1.00 12.80
ATOM 295 O PHE 177 24.366 21.842 47.845 1.00 14.50
ATOM 296 N ARG 178 22.945 23.258 46.803 1.00 8.14
ATOM 297 CA ARG 178 22.790 22.438 45.617 1.00 9.25
ATOM 298 CB ARG 178 21.344 21.949 45.519 1.00 15.01
ATOM 299 CG ARG 178 20.983 20.981 46.652 1.00 22.66
ATOM 300 CD ARG 178 19.910 19.993 46.265 1.00 28.20
ATOM 301 NE ARG 178 20.264 19.281 45.043 1.00 30.10
ATOM 302 CZ ARG 178 19.399 18.961 44.086 1.00 30.96
ATOM 303 NH1 ARG 178 18.113 19.293 44.219 1.00 25.66
ATOM 304 NH2 ARG 178 19.823 18.340 42.983 1.00 28.72
ATOM 305 C ARG 178 23.204 23.257 44.386 1.00 9.34

ATOM 306 O ARG 178 23.174 24.488 44.418 1.00 8.16
ATOM 307 N ALA 179 23.657 22.589 43.329 1.00 7.60
ATOM 308 CA ALA 179 24.069 23.290 42.117 1.00 6.68
ATOM 309 CB ALA 179 24.734 22.320 41.146 1.00 7.71
ATOM 310 C ALA 179 22.871 23.972 41.465 1.00 7.17
ATOM 311 O ALA 179 21.780 23.405 41.399 1.00 8.52
ATOM 312 N PHE 180 23.092 25.211 41.021 1.00 6.55
ATOM 313 CA PHE 180 22.102 26.061 40.349 1.00 8.23
ATOM 314 CB PHE 180 22.610 27.523 40.456 1.00 7.58
ATOM 315 CG PHE 180 21.645 28.583 39.950 1.00 7.95
ATOM 316 CD1 PHE 180 20.580 29.029 40.743 1.00 10.05
ATOM 317 CD2 PHE 180 21.839 29.173 38.705 1.00 10.04
ATOM 318 CE1 PHE 180 19.726 30.065 40.304 1.00 13.92
ATOM 319 CE2 PHE 180 20.998 30.204 38.262 1.00 12.57
ATOM 320 CZ PHE 180 19.940 30.650 39.070 1.00 10.87
ATOM 321 C PHE 180 22.040 25.592 38.873 1.00 7.43
ATOM 322 O PHE 180 22.592 26.229 37.981 1.00 8.61
ATOM 323 N LEU 181 21.404 24.452 38.630 1.00 7.22
ATOM 324 CA LEU 181 21.333 23.894 37.285 1.00 6.87
ATOM 325 CB LEU 181 22.520 22.923 37.065 1.00 8.00
ATOM 326 CG LEU 181 23.990 23.348 37.182 1.00 6.24
ATOM 327 CD1 LEU 181 24.918 22.140 37.255 1.00 6.93
ATOM 328 CD2 LEU 181 24.347 24.231 35.999 1.00 9.85
ATOM 329 C LEU 181 20.083 23.039 37.145 1.00 9.21
ATOM 330 O LEU 181 19.619 22.465 38.133 1.00 9.14
ATOM 331 N SER 182 19.506 22.993 35.941 1.00 7.07
ATOM 332 CA SER 182 18.403 22.062 35.686 1.00 7.88
ATOM 333 CB SER 182 17.500 22.550 34.551 1.00 8.40
ATOM 334 OG SER 182 16.552 23.491 35.006 1.00 8.46
ATOM 335 C SER 182 19.114 20.774 35.226 1.00 10.02
ATOM 336 O SER 182 20.248 20.825 34.737 1.00 11.73
ATOM 337 N SER 183 18.476 19.623 35.390 1.00 9.61
ATOM 338 CA SER 183 19.070 18.365 34.937 1.00 10.74
ATOM 339 CB SER 183 19.908 17.707 36.044 1.00 16.99
ATOM 340 OG SER 183 19.155 17.500 37.243 1.00 22.50
ATOM 341 C SER 183 17.933 17.458 34.462 1.00 10.89
ATOM 342 O SER 183 16.777 17.857 34.491 1.00 10.38
ATOM 343 N ARG 184 18.257 16.243 34.033 1.00 13.32
ATOM 344 CA ARG 184 17.235 15.336 33.520 1.00 13.60
ATOM 345 CB ARG 184 17.844 13.957 33.217 1.00 21.11
ATOM 346 CG ARG 184 16.818 12.903 32.776 1.00 31.07
ATOM 347 CD ARG 184 17.484 11.718 32.074 1.00 51.84
ATOM 348 NE ARG 184 18.168 12.133 30.839 1.00 75.25
ATOM 349 CZ ARG 184 17.571 12.370 29.663 1.00 83.77
ATOM 350 NH1 ARG 184 16.250 12.227 29.524 1.00 84.96
ATOM 351 NH2 ARG 184 18.293 12.812 28.633 1.00 85.63
ATOM 352 C ARG 184 15.969 15.175 34.356 1.00 12.92
ATOM 353 O ARG 184 14.867 15.231 33.822 1.00 16.34
ATOM 354 N LEU 185 16.125 14.990 35.663 1.00 12.43
ATOM 355 CA LEU 185 14.984 14.788 36.550 1.00 15.55
ATOM 356 CB LEU 185 15.285 13.613 37.466 1.00 17.61
ATOM 357 CG LEU 185 15.577 12.307 36.755 1.00 22.06
ATOM 358 CD1 LEU 185 16.091 11.332 37.798 1.00 23.60

ATOM 359 CD2 LEU 185 14.308 11.791 36.064 1.00 23.85
ATOM 360 C LEU 185 14.647 15.979 37.439 1.00 15.27
ATOM 361 O LEU 185 13.753 15.900 38.280 1.00 17.36
ATOM 362 N GLN 186 15.258 17.119 37.182 1.00 12.21
ATOM 363 CA GLN 186 15.048 18.245 38.060 1.00 13.64
ATOM 364 CB GLN 186 16.195 18.224 39.090 1.00 22.75
ATOM 365 CG GLN 186 16.299 19.426 39.993 1.00 37.49
ATOM 366 CD GLN 186 15.537 19.254 41.288 1.00 46.69
ATOM 367 OE1 GLN 186 16.072 18.714 42.266 1.00 52.06
ATOM 368 NE2 GLN 186 14.304 19.761 41.331 1.00 48.85
ATOM 369 C GLN 186 15.033 19.599 37.369 1.00 11.79
ATOM 370 O GLN 186 15.936 19.909 36.610 1.00 14.24
ATOM 371 N ASP 187 13.988 20.379 37.606 1.00 10.45
ATOM 372 CA ASP 187 13.926 21.736 37.076 1.00 10.04
ATOM 373 CB ASP 187 12.486 22.228 36.988 1.00 13.26
ATOM 374 CG ASP 187 11.684 21.479 35.970 1.00 15.08
ATOM 375 OD1 ASP 187 12.185 21.293 34.844 1.00 14.31
ATOM 376 OD2 ASP 187 10.555 21.063 36.287 1.00 21.37
ATOM 377 C ASP 187 14.640 22.598 38.120 1.00 10.87
ATOM 378 O ASP 187 14.478 22.398 39.326 1.00 11.85
ATOM 379 N LEU 188 15.442 23.544 37.664 1.00 10.75
ATOM 380 CA LEU 188 16.157 24.450 38.559 1.00 8.93
ATOM 381 CB LEU 188 16.853 25.524 37.723 1.00 9.42
ATOM 382 CG LEU 188 17.432 26.782 38.380 1.00 11.08
ATOM 383 CD1 LEU 188 18.419 26.387 39.464 1.00 14.34
ATOM 384 CD2 LEU 188 18.133 27.607 37.298 1.00 13.25
ATOM 385 C LEU 188 15.177 25.122 39.538 1.00 10.07
ATOM 386 O LEU 188 15.459 25.248 40.731 1.00 10.11
ATOM 387 N TYR 189 14.009 25.506 39.037 1.00 8.69
ATOM 388 CA TYR 189 13.022 26.183 39.878 1.00 10.49
ATOM 389 CB TYR 189 11.753 26.502 39.075 1.00 10.54
ATOM 390 CG TYR 189 10.717 27.195 39.926 1.00 17.51
ATOM 391 CD1 TYR 189 10.844 28.552 40.265 1.00 17.16
ATOM 392 CE1 TYR 189 9.911 29.177 41.105 1.00 17.25
ATOM 393 CD2 TYR 189 9.628 26.484 40.438 1.00 19.22
ATOM 394 CE2 TYR 189 8.700 27.097 41.274 1.00 21.20
ATOM 395 CZ TYR 189 8.847 28.436 41.604 1.00 20.23
ATOM 396 OH TYR 189 7.917 28.986 42.442 1.00 17.62
ATOM 397 C TYR 189 12.648 25.454 41.171 1.00 11.00
ATOM 398 O TYR 189 12.494 26.073 42.227 1.00 11.72
ATOM 399 N SER 190 12.554 24.133 41.090 1.00 10.73
ATOM 400 CA SER 190 12.150 23.295 42.213 1.00 9.77
ATOM 401 CB SER 190 11.622 21.972 41.674 1.00 13.82
ATOM 402 OG SER 190 10.448 22.187 40.921 1.00 28.12
ATOM 403 C SER 190 13.176 22.975 43.261 1.00 10.02
ATOM 404 O SER 190 12.835 22.339 44.259 1.00 12.81
ATOM 405 N ILE 191 14.421 23.395 43.054 1.00 10.13
ATOM 406 CA ILE 191 15.517 23.102 43.982 1.00 11.69
ATOM 407 CB ILE 191 16.877 23.514 43.386 1.00 12.50
ATOM 408 CG2 ILE 191 17.960 23.455 44.434 1.00 22.45
ATOM 409 CG1 ILE 191 17.239 22.597 42.223 1.00 14.35
ATOM 410 CD1 ILE 191 18.549 22.986 41.579 1.00 19.08
ATOM 411 C ILE 191 15.353 23.726 45.373 1.00 16.53

ATOM 412 O ILE 191 15.811 23.147 46.364 1.00 17.93
ATOM 413 N VAL 192 14.756 24.916 45.436 1.00 14.25
ATOM 414 CA VAL 192 14.513 25.599 46.708 1.00 13.18
ATOM 415 CB VAL 192 14.528 27.142 46.515 1.00 10.04
ATOM 416 CG1 VAL 192 13.966 27.853 47.745 1.00 11.77
ATOM 417 CG2 VAL 192 15.965 27.603 46.235 1.00 11.81
ATOM 418 C VAL 192 13.168 25.137 47.280 1.00 13.46
ATOM 419 O VAL 192 12.185 25.069 46.546 1.00 14.59
ATOM 420 N ARG 193 13.150 24.777 48.567 1.00 15.32
ATOM 421 CA ARG 193 11.933 24.305 49.256 1.00 15.89
ATOM 422 CB ARG 193 12.159 24.211 50.775 1.00 20.17
ATOM 423 CG ARG 193 13.164 23.153 51.232 0.00 17.65
ATOM 424 CD ARG 193 12.731 21.734 50.874 0.00 16.70
ATOM 425 NE ARG 193 13.064 21.385 49.496 0.00 15.78
ATOM 426 CZ ARG 193 14.272 20.998 49.093 0.00 15.27
ATOM 427 NH1 ARG 193 15.276 20.901 49.960 0.00 15.06
ATOM 428 NH2 ARG 193 14.477 20.727 47.815 0.00 15.06
ATOM 429 C ARG 193 10.784 25.248 48.983 1.00 17.12
ATOM 430 O ARG 193 10.948 26.470 49.038 1.00 16.17
ATOM 431 N ARG 194 9.609 24.678 48.732 1.00 17.83
ATOM 432 CA ARG 194 8.419 25.468 48.408 1.00 19.92
ATOM 433 CB ARG 194 7.180 24.560 48.282 1.00 21.81
ATOM 434 CG ARG 194 5.877 25.289 48.014 0.00 19.23
ATOM 435 CD ARG 194 4.722 24.309 47.932 0.00 17.77
ATOM 436 NE ARG 194 3.438 24.985 47.772 0.00 16.39
ATOM 437 CZ ARG 194 2.317 24.382 47.384 0.00 15.52
ATOM 438 NH1 ARG 194 2.316 23.080 47.111 0.00 15.16
ATOM 439 NH2 ARG 194 1.193 25.079 47.280 0.00 15.16
ATOM 440 C ARG 194 8.145 26.620 49.377 1.00 19.00
ATOM 441 O ARG 194 7.823 27.734 48.951 1.00 18.27
ATOM 442 N ALA 195 8.308 26.361 50.671 1.00 18.54
ATOM 443 CA ALA 195 8.059 27.384 51.675 1.00 18.53
ATOM 444 CB ALA 195 8.064 26.765 53.048 1.00 20.42
ATOM 445 C ALA 195 9.016 28.576 51.630 1.00 19.26
ATOM 446 O ALA 195 8.679 29.659 52.117 1.00 21.44
ATOM 447 N ASP 196 10.171 28.404 50.998 1.00 15.48
ATOM 448 CA ASP 196 11.154 29.473 50.929 1.00 14.34
ATOM 449 CB ASP 196 12.541 28.927 51.279 1.00 14.53
ATOM 450 CG ASP 196 12.634 28.446 52.714 1.00 25.06
ATOM 451 OD1 ASP 196 11.932 29.008 53.577 1.00 31.54
ATOM 452 OD2 ASP 196 13.390 27.497 52.979 1.00 23.54
ATOM 453 C ASP 196 11.230 30.158 49.585 1.00 13.66
ATOM 454 O ASP 196 12.082 31.008 49.385 1.00 16.79
ATOM 455 N ARG 197 10.314 29.849 48.678 1.00 13.68
ATOM 456 CA ARG 197 10.359 30.429 47.340 1.00 12.56
ATOM 457 CB ARG 197 9.655 29.505 46.353 1.00 11.95
ATOM 458 CG ARG 197 10.266 28.145 46.232 1.00 11.67
ATOM 459 CD ARG 197 9.529 27.313 45.206 1.00 16.62
ATOM 460 NE ARG 197 10.017 25.945 45.257 1.00 19.60
ATOM 461 CZ ARG 197 9.342 24.878 44.843 1.00 21.25
ATOM 462 NH1 ARG 197 8.123 25.013 44.336 1.00 22.10
ATOM 463 NH2 ARG 197 9.901 23.672 44.918 1.00 19.31
ATOM 464 C ARG 197 9.785 31.824 47.152 1.00 14.21

ATOM 465 O ARG 197 10.253 32.574 46.308 1.00 12.84
ATOM 466 N GLY 198 8.812 32.200 47.968 1.00 16.37
ATOM 467 CA GLY 198 8.174 33.474 47.737 1.00 15.07
ATOM 468 C GLY 198 8.604 34.693 48.499 1.00 17.12
ATOM 469 O GLY 198 8.419 35.796 48.007 1.00 21.05
ATOM 470 N SER 199 9.217 34.543 49.655 1.00 17.39
ATOM 471 CA SER 199 9.544 35.745 50.377 1.00 20.73
ATOM 472 CB SER 199 8.390 36.084 51.313 1.00 28.27
ATOM 473 OG SER 199 8.143 34.981 52.162 1.00 37.53
ATOM 474 C SER 199 10.831 35.719 51.146 1.00 20.82
ATOM 475 O SER 199 10.973 36.435 52.137 1.00 22.75
ATOM 476 N VAL 200 11.770 34.888 50.716 1.00 16.33
ATOM 477 CA VAL 200 13.058 34.837 51.383 1.00 13.69
ATOM 478 CB VAL 200 13.466 33.388 51.750 1.00 13.63
ATOM 479 CG1 VAL 200 14.843 33.377 52.360 1.00 11.91
ATOM 480 CG2 VAL 200 12.471 32.792 52.752 1.00 15.70
ATOM 481 C VAL 200 14.090 35.490 50.441 1.00 12.91
ATOM 482 O VAL 200 14.311 35.020 49.328 1.00 11.93
ATOM 483 N PRO 201 14.680 36.623 50.847 1.00 10.78
ATOM 484 CD PRO 201 14.477 37.430 52.062 1.00 9.78
ATOM 485 CA PRO 201 15.655 37.246 49.959 1.00 11.08
ATOM 486 CB PRO 201 16.067 38.511 50.723 1.00 11.01
ATOM 487 CG PRO 201 15.763 38.210 52.136 1.00 16.40
ATOM 488 C PRO 201 16.851 36.376 49.606 1.00 9.78
ATOM 489 O PRO 201 17.291 35.556 50.404 1.00 10.76
ATOM 490 N ILE 202 17.348 36.549 48.387 1.00 9.72
ATOM 491 CA ILE 202 18.528 35.831 47.913 1.00 11.47
ATOM 492 CB ILE 202 18.423 35.467 46.407 1.00 12.59
ATOM 493 CG2 ILE 202 19.674 34.695 45.956 1.00 10.13
ATOM 494 CG1 ILE 202 17.118 34.681 46.131 1.00 12.81
ATOM 495 CD1 ILE 202 16.991 33.329 46.828 1.00 12.75
ATOM 496 C ILE 202 19.690 36.800 48.099 1.00 9.90
ATOM 497 O ILE 202 19.632 37.939 47.633 1.00 9.51
ATOM 498 N VAL 203 20.743 36.345 48.770 1.00 8.31
ATOM 499 CA VAL 203 21.907 37.184 49.053 1.00 8.59
ATOM 500 CB VAL 203 22.029 37.520 50.603 1.00 9.06
ATOM 501 CG1 VAL 203 20.739 38.145 51.114 1.00 9.64
ATOM 502 CG2 VAL 203 22.381 36.272 51.424 1.00 10.29
ATOM 503 C VAL 203 23.184 36.488 48.628 1.00 8.32
ATOM 504 O VAL 203 23.194 35.274 48.402 1.00 9.94
ATOM 505 N ASN 204 24.246 37.260 48.462 1.00 7.22
ATOM 506 CA ASN 204 25.530 36.669 48.126 1.00 6.18
ATOM 507 CB ASN 204 26.384 37.605 47.253 1.00 7.17
ATOM 508 CG ASN 204 26.786 38.882 47.957 1.00 10.87
ATOM 509 OD1 ASN 204 26.814 38.957 49.189 1.00 10.05
ATOM 510 ND2 ASN 204 27.170 39.877 47.172 1.00 11.25
ATOM 511 C ASN 204 26.246 36.210 49.419 1.00 7.48
ATOM 512 O ASN 204 25.678 36.301 50.517 1.00 8.60
ATOM 513 N LEU 205 27.477 35.722 49.284 1.00 8.24
ATOM 514 CA LEU 205 28.260 35.223 50.406 1.00 10.00
ATOM 515 CB LEU 205 29.650 34.835 49.911 1.00 11.80
ATOM 516 CG LEU 205 30.610 34.229 50.944 1.00 13.04
ATOM 517 CD1 LEU 205 30.155 32.829 51.290 1.00 19.40

ATOM 518 CD2 LEU 205 32.037 34.215 50.398 1.00 14.64
ATOM 519 C LEU 205 28.387 36.242 51.543 1.00 12.19
ATOM 520 O LEU 205 28.441 35.864 52.716 1.00 13.21
ATOM 521 N LYS 206 28.481 37.519 51.175 1.00 10.81
ATOM 522 CA LYS 206 28.623 38.622 52.127 1.00 13.25
ATOM 523 CB LYS 206 29.507 39.717 51.528 1.00 13.08
ATOM 524 CG LYS 206 30.959 39.260 51.291 1.00 23.58
ATOM 525 CD LYS 206 31.813 40.348 50.659 1.00 35.02
ATOM 526 CE LYS 206 33.304 40.035 50.793 1.00 46.91
ATOM 527 NZ LYS 206 33.658 38.654 50.333 1.00 57.40
ATOM 528 C LYS 206 27.285 39.209 52.582 1.00 15.01
ATOM 529 O LYS 206 27.246 40.297 53.166 1.00 14.89
ATOM 530 N ASP 207 26.204 38.476 52.339 1.00 10.24
ATOM 531 CA ASP 207 24.858 38.886 52.720 1.00 10.26
ATOM 532 CB ASP 207 24.701 39.036 54.251 1.00 10.80
ATOM 533 CG ASP 207 24.771 37.710 54.988 1.00 16.79
ATOM 534 OD1 ASP 207 24.694 36.645 54.362 1.00 16.98
ATOM 535 OD2 ASP 207 24.896 37.720 56.222 1.00 19.23
ATOM 536 C ASP 207 24.309 40.113 52.011 1.00 11.53
ATOM 537 O ASP 207 23.379 40.748 52.505 1.00 14.87
ATOM 538 N GLU 208 24.880 40.461 50.864 1.00 9.33
ATOM 539 CA GLU 208 24.374 41.586 50.078 1.00 9.28
ATOM 540 CB GLU 208 25.459 42.094 49.144 1.00 10.70
ATOM 541 CG GLU 208 26.664 42.535 49.953 1.00 13.38
ATOM 542 CD GLU 208 27.861 42.970 49.142 1.00 22.15
ATOM 543 OE1 GLU 208 28.047 42.537 47.967 1.00 15.62
ATOM 544 OE2 GLU 208 28.648 43.754 49.722 1.00 27.12
ATOM 545 C GLU 208 23.177 41.063 49.301 1.00 11.06
ATOM 546 O GLU 208 23.246 39.999 48.658 1.00 10.86
ATOM 547 N VAL 209 22.063 41.779 49.394 1.00 9.59
ATOM 548 CA VAL 209 20.829 41.352 48.756 1.00 10.86
ATOM 549 CB VAL 209 19.620 42.141 49.290 1.00 11.29
ATOM 550 CG1 VAL 209 18.313 41.594 48.704 1.00 11.00
ATOM 551 CG2 VAL 209 19.607 42.087 50.813 1.00 11.82
ATOM 552 C VAL 209 20.887 41.425 47.251 1.00 13.44
ATOM 553 O VAL 209 21.249 42.465 46.687 1.00 14.37
ATOM 554 N LEU 210 20.555 40.302 46.610 1.00 10.99
ATOM 555 CA LEU 210 20.567 40.180 45.143 1.00 11.77
ATOM 556 CB LEU 210 21.245 38.868 44.717 1.00 10.60
ATOM 557 CG LEU 210 22.655 38.615 45.248 1.00 11.69
ATOM 558 CD1 LEU 210 23.111 37.258 44.788 1.00 15.27
ATOM 559 CD2 LEU 210 23.621 39.672 44.783 1.00 15.32
ATOM 560 C LEU 210 19.174 40.221 44.541 1.00 11.30
ATOM 561 O LEU 210 18.970 40.777 43.469 1.00 13.41
ATOM 562 N SER 211 18.218 39.620 45.230 1.00 12.59
ATOM 563 CA SER 211 16.843 39.560 44.748 1.00 12.51
ATOM 564 CB SER 211 16.700 38.362 43.783 1.00 12.81
ATOM 565 OG SER 211 15.363 38.168 43.380 1.00 17.30
ATOM 566 C SER 211 15.924 39.402 45.962 1.00 12.70
ATOM 567 O SER 211 16.319 38.822 46.978 1.00 13.12
ATOM 568 N PRO 212 14.701 39.966 45.890 1.00 12.25
ATOM 569 CD PRO 212 14.207 40.842 44.810 1.00 13.48
ATOM 570 CA PRO 212 13.734 39.876 46.995 1.00 12.35

ATOM 571 CB PRO 212 12.603 40.813 46.544 1.00 14.48
ATOM 572 CG PRO 212 12.730 40.829 45.043 1.00 13.98
ATOM 573 C PRO 212 13.230 38.466 47.303 1.00 11.21
ATOM 574 O PRO 212 12.808 38.179 48.430 1.00 13.32
ATOM 575 N SER 213 13.322 37.575 46.322 1.00 10.85
ATOM 576 CA SER 213 12.877 36.199 46.494 1.00 9.69
ATOM 577 CB SER 213 11.347 36.119 46.500 1.00 12.14
ATOM 578 OG SER 213 10.833 36.434 45.216 1.00 12.73
ATOM 579 C SER 213 13.373 35.340 45.347 1.00 10.77
ATOM 580 O SER 213 13.870 35.834 44.334 1.00 11.42
ATOM 581 N TRP 214 13.201 34.039 45.516 1.00 11.69
ATOM 582 CA TRP 214 13.573 33.052 44.512 1.00 11.56
ATOM 583 CB TRP 214 13.429 31.661 45.138 1.00 12.36
ATOM 584 CG TRP 214 13.706 30.501 44.220 1.00 11.79
ATOM 585 CD2 TRP 214 14.992 30.059 43.744 1.00 10.04
ATOM 586 CE2 TRP 214 14.784 28.837 43.053 1.00 10.39
ATOM 587 CE3 TRP 214 16.299 30.572 43.844 1.00 9.25
ATOM 588 CD1 TRP 214 12.798 29.570 43.782 1.00 12.27
ATOM 589 NE1 TRP 214 13.437 28.571 43.089 1.00 10.10
ATOM 590 CZ2 TRP 214 15.839 28.115 42.460 1.00 9.77
ATOM 591 CZ3 TRP 214 17.347 29.861 43.255 1.00 10.46
ATOM 592 CH2 TRP 214 17.108 28.638 42.572 1.00 10.11
ATOM 593 C TRP 214 12.629 33.202 43.317 1.00 10.01
ATOM 594 O TRP 214 13.063 33.291 42.172 1.00 11.47
ATOM 595 N ASP 215 11.335 33.305 43.601 1.00 10.89
ATOM 596 CA ASP 215 10.323 33.438 42.557 1.00 11.93
ATOM 597 CB ASP 215 8.926 33.600 43.165 1.00 12.37
ATOM 598 CG ASP 215 8.324 32.292 43.599 1.00 21.53
ATOM 599 OD1 ASP 215 8.934 31.235 43.333 1.00 21.13
ATOM 600 OD2 ASP 215 7.234 32.330 44.212 1.00 25.53
ATOM 601 C ASP 215 10.583 34.601 41.629 1.00 11.83
ATOM 602 O ASP 215 10.324 34.512 40.433 1.00 14.03
ATOM 603 N SER 216 11.074 35.703 42.179 1.00 12.12
ATOM 604 CA SER 216 11.343 36.893 41.375 1.00 15.57
ATOM 605 CB SER 216 11.925 38.008 42.250 1.00 17.98
ATOM 606 OG SER 216 11.019 38.315 43.287 1.00 37.82
ATOM 607 C SER 216 12.284 36.624 40.217 1.00 13.80
ATOM 608 O SER 216 12.184 37.253 39.164 1.00 16.51
ATOM 609 N LEU 217 13.204 35.687 40.405 1.00 13.84
ATOM 610 CA LEU 217 14.159 35.361 39.349 1.00 16.15
ATOM 611 CB LEU 217 15.291 34.483 39.905 1.00 13.80
ATOM 612 CG LEU 217 16.230 35.009 40.991 1.00 16.30
ATOM 613 CD1 LEU 217 17.166 33.873 41.400 1.00 18.85
ATOM 614 CD2 LEU 217 17.033 36.196 40.491 1.00 19.33
ATOM 615 C LEU 217 13.518 34.633 38.162 1.00 15.00
ATOM 616 O LEU 217 13.995 34.730 37.028 1.00 15.72
ATOM 617 N PHE 218 12.422 33.931 38.427 1.00 14.28
ATOM 618 CA PHE 218 11.764 33.113 37.411 1.00 15.74
ATOM 619 CB PHE 218 11.556 31.698 37.989 1.00 12.34
ATOM 620 CG PHE 218 12.820 31.081 38.495 1.00 12.47
ATOM 621 CD1 PHE 218 13.152 31.151 39.853 1.00 12.13
ATOM 622 CD2 PHE 218 13.715 30.476 37.607 1.00 11.71
ATOM 623 CE1 PHE 218 14.353 30.645 40.317 1.00 12.68

ATOM 624 CE2 PHE 218 14.934 29.959 38.064 1.00 12.62
ATOM 625 CZ PHE 218 15.260 30.044 39.427 1.00 11.54
ATOM 626 C PHE 218 10.462 33.673 36.872 1.00 19.66
ATOM 627 O PHE 218 9.680 32.961 36.240 1.00 19.44
ATOM 628 N SER 219 10.291 34.979 37.037 1.00 20.96
ATOM 629 CA SER 219 9.092 35.704 36.612 1.00 20.25
ATOM 630 CB SER 219 9.107 37.069 37.285 1.00 18.96
ATOM 631 OG SER 219 10.301 37.740 36.904 1.00 24.95
ATOM 632 C SER 219 9.013 35.941 35.103 1.00 19.87
ATOM 633 O SER 219 7.959 36.318 34.565 1.00 20.23
ATOM 634 N GLY 220 10.151 35.817 34.439 1.00 16.90
ATOM 635 CA GLY 220 10.200 36.063 33.015 1.00 18.69
ATOM 636 C GLY 220 11.197 37.177 32.734 1.00 19.82
ATOM 637 O GLY 220 11.512 37.439 31.586 1.00 22.45
ATOM 638 N SER 221 11.718 37.801 33.791 1.00 20.73
ATOM 639 CA SER 221 12.703 38.891 33.692 1.00 20.97
ATOM 640 CB SER 221 12.840 39.571 35.057 1.00 18.70
ATOM 641 OG SER 221 13.371 38.657 36.017 1.00 29.42
ATOM 642 C SER 221 14.084 38.349 33.294 1.00 20.66
ATOM 643 O SER 221 15.019 39.120 33.039 1.00 19.09
ATOM 644 N GLN 222 14.212 37.022 33.324 1.00 15.11
ATOM 645 CA GLN 222 15.450 36.314 33.011 1.00 14.71
ATOM 646 CB GLN 222 16.056 36.757 31.663 1.00 16.07
ATOM 647 CG GLN 222 15.106 36.574 30.479 1.00 23.55
ATOM 648 CD GLN 222 15.802 36.549 29.147 1.00 27.05
ATOM 649 OE1 GLN 222 16.784 37.258 28.932 1.00 39.97
ATOM 650 NE2 GLN 222 15.289 35.742 28.229 1.00 34.40
ATOM 651 C GLN 222 16.479 36.423 34.142 1.00 13.28
ATOM 652 O GLN 222 17.682 36.457 33.883 1.00 13.22
ATOM 653 N GLY 223 15.993 36.452 35.390 1.00 12.76
ATOM 654 CA GLY 223 16.862 36.522 36.562 1.00 11.74
ATOM 655 C GLY 223 17.691 37.782 36.642 1.00 12.55
ATOM 656 O GLY 223 18.902 37.746 36.884 1.00 10.85
ATOM 657 N GLN 224 17.025 38.906 36.408 1.00 15.41
ATOM 658 CA GLN 224 17.656 40.215 36.425 1.00 18.36
ATOM 659 CB GLN 224 16.651 41.251 35.899 1.00 24.28
ATOM 660 CG GLN 224 17.165 42.686 35.786 1.00 30.95
ATOM 661 CD GLN 224 18.211 42.865 34.703 1.00 37.18
ATOM 662 OE1 GLN 224 19.411 42.959 34.987 1.00 41.40
ATOM 663 NE2 GLN 224 17.764 42.923 33.451 1.00 34.95
ATOM 664 C GLN 224 18.137 40.593 37.826 1.00 19.75
ATOM 665 O GLN 224 17.386 40.504 38.802 1.00 23.25
ATOM 666 N LEU 225 19.408 40.945 37.939 1.00 18.83
ATOM 667 CA LEU 225 19.937 41.357 39.226 1.00 23.64
ATOM 668 CB LEU 225 21.302 40.733 39.510 1.00 23.44
ATOM 669 CG LEU 225 21.418 39.204 39.546 1.00 21.44
ATOM 670 CD1 LEU 225 22.849 38.826 39.846 1.00 30.04
ATOM 671 CD2 LEU 225 20.493 38.586 40.573 1.00 23.51
ATOM 672 C LEU 225 20.052 42.864 39.183 1.00 26.18
ATOM 673 O LEU 225 20.007 43.469 38.120 1.00 27.58
ATOM 674 N GLN 226 20.094 43.482 40.349 1.00 33.02
ATOM 675 CA GLN 226 20.221 44.928 40.404 1.00 35.26
ATOM 676 CB GLN 226 19.951 45.420 41.819 1.00 41.02

ATOM 677 CG GLN 226 19.221 46.746 41.863 1.00 50.30
ATOM 678 CD GLN 226 19.298 47.404 43.206 1.00 62.18
ATOM 679 OE1 GLN 226 18.313 47.447 43.936 1.00 69.77
ATOM 680 NE2 GLN 226 20.469 47.930 43.545 1.00 63.73
ATOM 681 C GLN 226 21.644 45.287 39.995 1.00 34.91
ATOM 682 O GLN 226 22.581 44.522 40.253 1.00 34.64
ATOM 683 N PRO 227 21.830 46.456 39.363 1.00 36.79
ATOM 684 CD PRO 227 20.802 47.459 39.025 1.00 40.94
ATOM 685 CA PRO 227 23.154 46.907 38.924 1.00 36.81
ATOM 686 CB PRO 227 22.898 48.354 38.471 1.00 38.12
ATOM 687 CG PRO 227 21.510 48.295 37.973 1.00 42.81
ATOM 688 C PRO 227 24.144 46.871 40.080 1.00 34.94
ATOM 689 O PRO 227 23.774 47.111 41.235 1.00 32.98
ATOM 690 N GLY 228 25.389 46.538 39.768 1.00 32.98
ATOM 691 CA GLY 228 26.408 46.504 40.796 1.00 30.54
ATOM 692 C GLY 228 26.394 45.263 41.658 1.00 28.50
ATOM 693 O GLY 228 27.285 45.110 42.497 1.00 30.52
ATOM 694 N ALA 229 25.384 44.404 41.486 1.00 25.56
ATOM 695 CA ALA 229 25.276 43.143 42.241 1.00 22.10
ATOM 696 CB ALA 229 24.112 42.296 41.705 1.00 21.32
ATOM 697 C ALA 229 26.581 42.383 42.058 1.00 18.87
ATOM 698 O ALA 229 27.128 42.367 40.964 1.00 21.82
ATOM 699 N ARG 230 27.092 41.799 43.134 1.00 16.13
ATOM 700 CA ARG 230 28.345 41.035 43.113 1.00 14.81
ATOM 701 CB ARG 230 29.321 41.571 44.160 1.00 14.64
ATOM 702 CG ARG 230 29.824 42.937 43.902 1.00 26.70
ATOM 703 CD ARG 230 30.941 43.241 44.854 1.00 26.86
ATOM 704 NE ARG 230 30.510 43.360 46.248 1.00 27.65
ATOM 705 CZ ARG 230 31.318 43.782 47.219 1.00 34.32
ATOM 706 NH1 ARG 230 32.573 44.110 46.922 1.00 31.38
ATOM 707 NH2 ARG 230 30.897 43.862 48.475 1.00 28.97
ATOM 708 C ARG 230 28.087 39.581 43.493 1.00 12.29
ATOM 709 O ARG 230 27.240 39.292 44.346 1.00 13.37
ATOM 710 N ILE 231 28.824 38.675 42.871 1.00 9.91
ATOM 711 CA ILE 231 28.706 37.271 43.217 1.00 10.26
ATOM 712 CB ILE 231 28.123 36.417 42.071 1.00 13.89
ATOM 713 CG2 ILE 231 28.197 34.914 42.441 1.00 13.66
ATOM 714 CG1 ILE 231 26.676 36.869 41.796 1.00 16.94
ATOM 715 CD1 ILE 231 25.967 36.091 40.731 1.00 20.65
ATOM 716 C ILE 231 30.091 36.795 43.600 1.00 9.79
ATOM 717 O ILE 231 31.062 37.018 42.874 1.00 10.47
ATOM 718 N PHE 232 30.188 36.265 44.813 1.00 10.02
ATOM 719 CA PHE 232 31.443 35.739 45.358 1.00 10.35
ATOM 720 CB PHE 232 31.621 36.196 46.818 1.00 8.78
ATOM 721 CG PHE 232 31.751 37.672 46.970 1.00 11.12
ATOM 722 CD1 PHE 232 30.638 38.464 47.202 1.00 12.05
ATOM 723 CD2 PHE 232 32.989 38.278 46.863 1.00 16.49
ATOM 724 CE1 PHE 232 30.763 39.839 47.316 1.00 19.05
ATOM 725 CE2 PHE 232 33.116 39.668 46.978 1.00 16.99
ATOM 726 CZ PHE 232 32.008 40.438 47.201 1.00 13.69
ATOM 727 C PHE 232 31.478 34.204 45.350 1.00 10.13
ATOM 728 O PHE 232 30.439 33.544 45.496 1.00 9.50
ATOM 729 N SER 233 32.680 33.658 45.186 1.00 9.09

ATOM 730 CA SER 233 32.895 32.219 45.259 1.00 8.23
ATOM 731 CB SER 233 34.207 31.869 44.581 1.00 7.47
ATOM 732 OG SER 233 35.280 32.544 45.204 1.00 11.40
ATOM 733 C SER 233 32.974 31.890 46.767 1.00 10.53
ATOM 734 O SER 233 33.031 32.816 47.602 1.00 9.05
ATOM 735 N PHE 234 33.020 30.600 47.111 1.00 8.96
ATOM 736 CA PHE 234 33.081 30.177 48.516 1.00 8.36
ATOM 737 CB PHE 234 33.069 28.647 48.630 1.00 8.82
ATOM 738 CG PHE 234 31.719 28.043 48.389 1.00 7.88
ATOM 739 CD1 PHE 234 31.414 27.451 47.162 1.00 9.14
ATOM 740 CD2 PHE 234 30.733 28.098 49.381 1.00 7.40
ATOM 741 CE1 PHE 234 30.146 26.927 46.924 1.00 9.95
ATOM 742 CE2 PHE 234 29.461 27.585 49.162 1.00 9.69
ATOM 743 CZ PHE 234 29.159 26.995 47.928 1.00 10.14
ATOM 744 C PHE 234 34.303 30.744 49.227 1.00 10.56
ATOM 745 O PHE 234 34.216 31.140 50.399 1.00 10.48
ATOM 746 N ASP 235 35.434 30.804 48.529 1.00 10.70
ATOM 747 CA ASP 235 36.644 31.338 49.139 1.00 11.77
ATOM 748 CB ASP 235 37.909 30.652 48.584 1.00 10.84
ATOM 749 CG ASP 235 38.130 30.903 47.097 1.00 16.86
ATOM 750 OD1 ASP 235 37.519 31.828 46.524 1.00 13.35
ATOM 751 OD2 ASP 235 38.933 30.152 46.491 1.00 21.65
ATOM 752 C ASP 235 36.761 32.878 49.123 1.00 13.33
ATOM 753 O ASP 235 37.852 33.423 49.350 1.00 15.58
ATOM 754 N GLY 236 35.651 33.557 48.817 1.00 9.84
ATOM 755 CA GLY 236 35.600 35.003 48.868 1.00 9.11
ATOM 756 C GLY 236 36.040 35.864 47.715 1.00 11.25
ATOM 757 O GLY 236 36.204 37.065 47.900 1.00 16.51
ATOM 758 N ARG 237 36.178 35.308 46.527 1.00 10.63
ATOM 759 CA ARG 237 36.584 36.099 45.372 1.00 10.06
ATOM 760 CB ARG 237 37.541 35.290 44.495 1.00 13.52
ATOM 761 CG ARG 237 38.918 35.068 45.112 1.00 13.17
ATOM 762 CD ARG 237 39.705 34.088 44.269 1.00 12.67
ATOM 763 NE ARG 237 39.162 32.749 44.416 1.00 14.67
ATOM 764 CZ ARG 237 39.238 31.785 43.506 1.00 17.38
ATOM 765 NH1 ARG 237 39.846 31.995 42.352 1.00 17.60
ATOM 766 NH2 ARG 237 38.696 30.605 43.753 1.00 20.61
ATOM 767 C ARG 237 35.404 36.570 44.524 1.00 11.45
ATOM 768 O ARG 237 34.431 35.825 44.327 1.00 10.90
ATOM 769 N ASP 238 35.469 37.820 44.063 1.00 10.87
ATOM 770 CA ASP 238 34.418 38.365 43.205 1.00 11.26
ATOM 771 CB ASP 238 34.500 39.894 43.168 1.00 12.93
ATOM 772 CG ASP 238 33.423 40.532 42.284 1.00 15.24
ATOM 773 OD1 ASP 238 32.990 39.961 41.268 1.00 14.40
ATOM 774 OD2 ASP 238 33.027 41.658 42.585 1.00 19.77
ATOM 775 C ASP 238 34.678 37.764 41.813 1.00 13.62
ATOM 776 O ASP 238 35.700 38.052 41.163 1.00 12.96
ATOM 777 N VAL 239 33.741 36.939 41.361 1.00 10.94
ATOM 778 CA VAL 239 33.868 36.241 40.088 1.00 12.62
ATOM 779 CB VAL 239 32.728 35.199 39.937 1.00 16.76
ATOM 780 CG1 VAL 239 31.396 35.879 39.691 1.00 14.71
ATOM 781 CG2 VAL 239 33.042 34.245 38.839 1.00 35.08
ATOM 782 C VAL 239 33.967 37.137 38.841 1.00 14.13

ATOM 783 O VAL 239 34.545 36.747 37.822 1.00 14.25
ATOM 784 N LEU 240 33.418 38.342 38.919 1.00 15.56
ATOM 785 CA LEU 240 33.481 39.256 37.783 1.00 18.76
ATOM 786 CB LEU 240 32.330 40.270 37.819 1.00 20.08
ATOM 787 CG LEU 240 31.783 40.672 36.446 1.00 28.99
ATOM 788 CD1 LEU 240 30.998 39.515 35.872 1.00 32.72
ATOM 789 CD2 LEU 240 30.894 41.884 36.569 1.00 34.23
ATOM 790 C LEU 240 34.826 39.993 37.733 1.00 21.57
ATOM 791 O LEU 240 35.367 40.230 36.652 1.00 23.34
ATOM 792 N ARG 241 35.407 40.268 38.897 1.00 20.15
ATOM 793 CA ARG 241 36.661 41.011 38.938 1.00 21.02
ATOM 794 CB ARG 241 36.657 41.976 40.128 1.00 22.27
ATOM 795 CG ARG 241 35.577 43.055 40.056 1.00 22.44
ATOM 796 CD ARG 241 35.646 43.973 41.260 0.00 20.57
ATOM 797 NE ARG 241 34.424 44.759 41.378 0.00 19.29
ATOM 798 CZ ARG 241 34.218 45.931 40.780 0.00 18.55
ATOM 799 NH1 ARG 241 35.163 46.476 40.020 0.00 18.26
ATOM 800 NH2 ARG 241 33.040 46.532 40.896 0.00 18.26
ATOM 801 C ARG 241 37.917 40.162 38.973 1.00 22.41
ATOM 802 O ARG 241 39.017 40.673 38.793 1.00 24.72
ATOM 803 N HIS 242 37.757 38.863 39.185 1.00 20.26
ATOM 804 CA HIS 242 38.898 37.972 39.280 1.00 19.34
ATOM 805 CB HIS 242 38.667 37.011 40.438 1.00 18.34
ATOM 806 CG HIS 242 39.922 36.428 40.971 1.00 23.21
ATOM 807 CD2 HIS 242 40.667 36.764 42.052 1.00 24.92
ATOM 808 ND1 HIS 242 40.585 35.392 40.349 1.00 27.01
ATOM 809 CE1 HIS 242 41.690 35.114 41.019 1.00 28.51
ATOM 810 NE2 HIS 242 41.761 35.933 42.058 1.00 29.24
ATOM 811 C HIS 242 39.216 37.205 37.989 1.00 17.20
ATOM 812 O HIS 242 38.362 36.526 37.437 1.00 17.26
ATOM 813 N PRO 243 40.484 37.199 37.563 1.00 17.89
ATOM 814 CD PRO 243 41.647 37.855 38.194 1.00 20.85
ATOM 815 CA PRO 243 40.875 36.500 36.330 1.00 16.49
ATOM 816 CB PRO 243 42.316 36.970 36.112 1.00 20.92
ATOM 817 CG PRO 243 42.822 37.158 37.525 1.00 19.91
ATOM 818 C PRO 243 40.754 34.969 36.294 1.00 18.47
ATOM 819 O PRO 243 40.859 34.371 35.216 1.00 19.70
ATOM 820 N ALA 244 40.498 34.344 37.450 1.00 15.25
ATOM 821 CA ALA 244 40.372 32.884 37.525 1.00 13.10
ATOM 822 CB ALA 244 40.299 32.415 38.971 1.00 14.32
ATOM 823 C ALA 244 39.166 32.384 36.735 1.00 12.10
ATOM 824 O ALA 244 39.062 31.198 36.433 1.00 16.31
ATOM 825 N TRP 245 38.236 33.288 36.448 1.00 11.10
ATOM 826 CA TRP 245 37.057 32.974 35.633 1.00 12.47
ATOM 827 CB TRP 245 35.765 33.331 36.371 1.00 11.95
ATOM 828 CG TRP 245 35.490 32.473 37.579 1.00 11.69
ATOM 829 CD2 TRP 245 35.919 32.721 38.930 1.00 11.65
ATOM 830 CE2 TRP 245 35.415 31.669 39.726 1.00 11.33
ATOM 831 CE3 TRP 245 36.674 33.730 39.540 1.00 11.70
ATOM 832 CD1 TRP 245 34.763 31.317 37.614 1.00 12.75
ATOM 833 NE1 TRP 245 34.716 30.833 38.901 1.00 15.29
ATOM 834 CZ2 TRP 245 35.643 31.594 41.098 1.00 10.78
ATOM 835 CZ3 TRP 245 36.903 33.660 40.910 1.00 13.94

ATOM 836 CH2 TRP 245 36.386 32.594 41.673 1.00 14.46
ATOM 837 C TRP 245 37.203 33.845 34.373 1.00 14.31
ATOM 838 O TRP 245 36.743 34.989 34.336 1.00 16.32
ATOM 839 N PRO 246 37.891 33.327 33.345 1.00 15.74
ATOM 840 CD PRO 246 38.521 31.997 33.265 1.00 18.39
ATOM 841 CA PRO 246 38.102 34.068 32.101 1.00 18.56
ATOM 842 CB PRO 246 38.990 33.124 31.294 1.00 19.24
ATOM 843 CG PRO 246 38.590 31.778 31.787 1.00 27.60
ATOM 844 C PRO 246 36.830 34.439 31.349 1.00 18.21
ATOM 845 O PRO 246 36.806 35.434 30.627 1.00 21.01
ATOM 846 N GLN 247 35.779 33.638 31.496 1.00 15.33
ATOM 847 CA GLN 247 34.520 33.930 30.825 1.00 15.65
ATOM 848 CB GLN 247 34.173 32.812 29.854 1.00 21.68
ATOM 849 CG GLN 247 35.265 32.635 28.812 1.00 29.04
ATOM 850 CD GLN 247 34.750 32.067 27.533 1.00 41.63
ATOM 851 OE1 GLN 247 34.307 32.830 26.627 1.00 54.44
ATOM 852 NE2 GLN 247 34.818 30.747 27.395 1.00 38.76
ATOM 853 C GLN 247 33.432 34.158 31.864 1.00 14.94
ATOM 854 O GLN 247 33.169 33.310 32.719 1.00 15.97
ATOM 855 N LYS 248 32.818 35.328 31.793 1.00 12.37
ATOM 856 CA LYS 248 31.813 35.726 32.761 1.00 10.26
ATOM 857 CB LYS 248 31.873 37.237 32.974 1.00 8.88
ATOM 858 CG LYS 248 33.286 37.766 33.167 1.00 10.72
ATOM 859 CD LYS 248 33.997 37.142 34.363 1.00 11.39
ATOM 860 CE LYS 248 35.366 37.783 34.502 1.00 12.62
ATOM 861 NZ LYS 248 36.167 37.202 35.606 1.00 13.55
ATOM 862 C LYS 248 30.387 35.257 32.484 1.00 11.42
ATOM 863 O LYS 248 29.427 36.023 32.651 1.00 14.70
ATOM 864 N SER 249 30.261 33.997 32.067 1.00 9.53
ATOM 865 CA SER 249 28.962 33.397 31.812 1.00 9.68
ATOM 866 CB SER 249 28.889 32.805 30.401 1.00 12.41
ATOM 867 OG SER 249 28.826 33.846 29.430 1.00 14.83
ATOM 868 C SER 249 28.729 32.323 32.876 1.00 8.86
ATOM 869 O SER 249 29.679 31.801 33.457 1.00 8.31
ATOM 870 N VAL 250 27.464 32.021 33.120 1.00 9.03
ATOM 871 CA VAL 250 27.055 31.044 34.123 1.00 10.67
ATOM 872 CB VAL 250 26.186 31.731 35.210 1.00 13.24
ATOM 873 CG1 VAL 250 25.716 30.713 36.238 1.00 16.31
ATOM 874 CG2 VAL 250 26.969 32.847 35.887 1.00 17.56
ATOM 875 C VAL 250 26.209 29.953 33.479 1.00 10.06
ATOM 876 O VAL 250 25.302 30.252 32.688 1.00 8.85
ATOM 877 N TRP 251 26.522 28.697 33.790 1.00 8.27
ATOM 878 CA TRP 251 25.748 27.559 33.273 1.00 7.25
ATOM 879 CB TRP 251 26.474 26.221 33.539 1.00 5.81
ATOM 880 CG TRP 251 27.668 25.919 32.689 1.00 8.44
ATOM 881 CD2 TRP 251 27.697 25.804 31.253 1.00 7.01
ATOM 882 CE2 TRP 251 29.014 25.442 30.891 1.00 8.05
ATOM 883 CE3 TRP 251 26.735 25.982 30.243 1.00 11.41
ATOM 884 CD1 TRP 251 28.937 25.639 33.122 1.00 7.73
ATOM 885 NE1 TRP 251 29.750 25.349 32.044 1.00 9.29
ATOM 886 CZ2 TRP 251 29.401 25.250 29.548 1.00 10.00
ATOM 887 CZ3 TRP 251 27.131 25.794 28.883 1.00 11.74
ATOM 888 CH2 TRP 251 28.447 25.431 28.569 1.00 8.88

ATOM 889 C TRP 251 24.426 27.471 34.026 1.00 7.43
ATOM 890 O TRP 251 24.381 27.713 35.231 1.00 8.02
ATOM 891 N HIS 252 23.345 27.143 33.328 1.00 6.15
ATOM 892 CA HIS 252 22.077 26.929 34.024 1.00 6.31
ATOM 893 CB HIS 252 21.299 28.233 34.291 1.00 8.14
ATOM 894 CG HIS 252 20.937 29.004 33.055 1.00 7.73
ATOM 895 CD2 HIS 252 21.407 30.176 32.565 1.00 9.83
ATOM 896 ND1 HIS 252 19.952 28.590 32.180 1.00 8.85
ATOM 897 CE1 HIS 252 19.834 29.477 31.199 1.00 8.72
ATOM 898 NE2 HIS 252 20.708 30.445 31.412 1.00 9.06
ATOM 899 C HIS 252 21.179 25.836 33.413 1.00 7.71
ATOM 900 O HIS 252 20.389 25.228 34.127 1.00 8.53
ATOM 901 N GLY 253 21.281 25.611 32.099 1.00 8.03
ATOM 902 CA GLY 253 20.474 24.592 31.430 1.00 7.38
ATOM 903 C GLY 253 18.968 24.738 31.580 1.00 8.73
ATOM 904 O GLY 253 18.253 23.743 31.447 1.00 10.24
ATOM 905 N SER 254 18.475 25.974 31.735 1.00 7.94
ATOM 906 CA SER 254 17.044 26.228 31.966 1.00 9.32
ATOM 907 CB SER 254 16.823 26.635 33.428 1.00 8.58
ATOM 908 OG SER 254 17.548 25.801 34.313 1.00 9.45
ATOM 909 C SER 254 16.414 27.333 31.135 1.00 9.44
ATOM 910 O SER 254 17.119 28.217 30.655 1.00 9.05
ATOM 911 N ASP 255 15.085 27.294 31.018 1.00 9.69
ATOM 912 CA ASP 255 14.370 28.355 30.328 1.00 10.56
ATOM 913 CB ASP 255 13.078 27.873 29.644 1.00 11.81
ATOM 914 CG ASP 255 11.970 27.480 30.603 1.00 16.63
ATOM 915 OD1 ASP 255 11.962 27.813 31.798 1.00 13.43
ATOM 916 OD2 ASP 255 11.042 26.822 30.125 1.00 20.81
ATOM 917 C ASP 255 14.159 29.484 31.357 1.00 12.19
ATOM 918 O ASP 255 14.563 29.347 32.517 1.00 8.72
ATOM 919 N PRO 256 13.535 30.616 30.949 1.00 12.50
ATOM 920 CD PRO 256 13.135 31.021 29.596 1.00 13.84
ATOM 921 CA PRO 256 13.338 31.716 31.911 1.00 13.68
ATOM 922 CB PRO 256 12.731 32.817 31.043 1.00 16.35
ATOM 923 CG PRO 256 13.291 32.514 29.670 1.00 18.75
ATOM 924 C PRO 256 12.501 31.437 33.141 1.00 14.48
ATOM 925 O PRO 256 12.577 32.183 34.125 1.00 16.99
ATOM 926 N SER 257 11.676 30.394 33.090 1.00 12.81
ATOM 927 CA SER 257 10.855 30.046 34.243 1.00 13.26
ATOM 928 CB SER 257 9.477 29.557 33.786 1.00 18.73
ATOM 929 OG SER 257 9.580 28.367 33.026 1.00 28.07
ATOM 930 C SER 257 11.537 28.987 35.128 1.00 11.91
ATOM 931 O SER 257 10.952 28.501 36.092 1.00 13.55
ATOM 932 N GLY 258 12.772 28.634 34.790 1.00 9.77
ATOM 933 CA GLY 258 13.508 27.654 35.563 1.00 10.17
ATOM 934 C GLY 258 13.238 26.204 35.211 1.00 12.95
ATOM 935 O GLY 258 13.517 25.312 36.023 1.00 12.41
ATOM 936 N ARG 259 12.664 25.952 34.039 1.00 11.66
ATOM 937 CA ARG 259 12.387 24.580 33.636 1.00 12.36
ATOM 938 CB ARG 259 11.078 24.502 32.860 1.00 15.24
ATOM 939 CG ARG 259 9.829 24.886 33.661 1.00 19.16
ATOM 940 CD ARG 259 8.609 24.876 32.766 0.00 16.18
ATOM 941 NE ARG 259 8.818 25.731 31.601 0.00 14.78

ATOM 942 CZ ARG 259 7.995 26.702 31.219 0.00 13.66
ATOM 943 NH1 ARG 259 6.890 26.949 31.912 0.00 13.15
ATOM 944 NH2 ARG 259 8.311 27.470 30.185 0.00 13.15
ATOM 945 C ARG 259 13.539 24.045 32.795 1.00 9.40
ATOM 946 O ARG 259 14.193 24.797 32.072 1.00 11.64
ATOM 947 N ARG 260 13.767 22.740 32.890 1.00 10.36
ATOM 948 CA ARG 260 14.859 22.072 32.208 1.00 10.92
ATOM 949 CB ARG 260 14.963 20.613 32.681 1.00 8.05
ATOM 950 CG ARG 260 13.903 19.681 32.102 1.00 13.57
ATOM 951 CD ARG 260 13.715 18.440 32.959 1.00 13.55
ATOM 952 NE ARG 260 12.793 18.708 34.059 1.00 14.10
ATOM 953 CZ ARG 260 12.264 17.784 34.852 1.00 15.72
ATOM 954 NH1 ARG 260 12.574 16.503 34.674 1.00 14.41
ATOM 955 NH2 ARG 260 11.392 18.141 35.792 1.00 16.24
ATOM 956 C ARG 260 14.762 22.116 30.691 1.00 11.29
ATOM 957 O ARG 260 13.659 22.063 30.137 1.00 13.57
ATOM 958 N LEU 261 15.916 22.281 30.043 1.00 10.67
ATOM 959 CA LEU 261 16.026 22.303 28.585 1.00 10.49
ATOM 960 CB LEU 261 16.766 23.557 28.106 1.00 11.75
ATOM 961 CG LEU 261 16.007 24.869 28.276 1.00 15.29
ATOM 962 CD1 LEU 261 16.865 26.025 27.794 1.00 14.39
ATOM 963 CD2 LEU 261 14.698 24.838 27.505 1.00 18.88
ATOM 964 C LEU 261 16.802 21.044 28.207 1.00 11.08
ATOM 965 O LEU 261 18.025 21.037 28.200 1.00 12.60
ATOM 966 N MET 262 16.078 19.970 27.897 1.00 13.03
ATOM 967 CA MET 262 16.694 18.697 27.572 1.00 15.60
ATOM 968 CB MET 262 15.635 17.618 27.430 1.00 21.23
ATOM 969 CG MET 262 14.861 17.413 28.728 1.00 42.59
ATOM 970 SD MET 262 13.990 15.830 28.827 1.00 54.60
ATOM 971 CE MET 262 14.754 15.114 30.316 1.00 55.07
ATOM 972 C MET 262 17.610 18.714 26.379 1.00 15.15
ATOM 973 O MET 262 18.499 17.880 26.283 1.00 18.38
ATOM 974 N GLU 263 17.431 19.681 25.490 1.00 12.77
ATOM 975 CA GLU 263 18.305 19.781 24.332 1.00 16.03
ATOM 976 CB GLU 263 17.535 20.228 23.087 1.00 20.28
ATOM 977 CG GLU 263 16.352 19.339 22.712 1.00 34.89
ATOM 978 CD GLU 263 16.755 17.925 22.342 1.00 42.80
ATOM 979 OE1 GLU 263 17.894 17.723 21.865 1.00 45.67
ATOM 980 OE2 GLU 263 15.918 17.014 22.527 1.00 55.63
ATOM 981 C GLU 263 19.433 20.770 24.597 1.00 17.27
ATOM 982 O GLU 263 20.280 20.998 23.730 1.00 16.53
ATOM 983 N SER 264 19.464 21.355 25.791 1.00 13.09
ATOM 984 CA SER 264 20.502 22.324 26.082 1.00 10.58
ATOM 985 CB SER 264 20.071 23.722 25.646 1.00 9.25
ATOM 986 OG SER 264 21.226 24.498 25.380 1.00 16.12
ATOM 987 C SER 264 20.995 22.332 27.528 1.00 10.61
ATOM 988 O SER 264 20.949 23.349 28.233 1.00 10.80
ATOM 989 N TYR 265 21.450 21.170 27.966 1.00 8.72
ATOM 990 CA TYR 265 22.023 21.048 29.289 1.00 10.84
ATOM 991 CB TYR 265 20.977 20.760 30.380 1.00 11.87
ATOM 992 CG TYR 265 20.152 19.491 30.297 1.00 8.78
ATOM 993 CD1 TYR 265 19.093 19.305 31.188 1.00 8.95
ATOM 994 CE1 TYR 265 18.308 18.157 31.162 1.00 11.41

ATOM 995 CD2 TYR 265 20.419 18.484 29.360 1.00 11.39
ATOM 996 CE2 TYR 265 19.634 17.313 29.326 1.00 12.07
ATOM 997 CZ TYR 265 18.585 17.164 30.234 1.00 17.30
ATOM 998 OH TYR 265 17.826 16.018 30.249 1.00 16.79
ATOM 999 C TYR 265 23.211 20.088 29.311 1.00 9.39
ATOM 1000 O TYR 265 23.467 19.382 30.293 1.00 8.37
ATOM 1001 N CYS 266 23.974 20.129 28.214 1.00 8.27
ATOM 1002 CA CYS 266 25.182 19.321 28.046 1.00 8.39
ATOM 1003 C CYS 266 24.988 17.852 28.419 1.00 7.82
ATOM 1004 O CYS 266 25.821 17.271 29.107 1.00 8.83
ATOM 1005 CB CYS 266 26.337 19.943 28.829 1.00 9.42
ATOM 1006 SG CYS 266 26.763 21.610 28.237 1.00 8.90
ATOM 1007 N GLU 267 23.880 17.276 27.953 1.00 8.61
ATOM 1008 CA GLU 267 23.544 15.882 28.221 1.00 11.70
ATOM 1009 CB GLU 267 24.482 14.981 27.419 1.00 12.76
ATOM 1010 CG GLU 267 24.305 15.265 25.908 1.00 24.58
ATOM 1011 CD GLU 267 25.377 14.673 25.007 1.00 39.48
ATOM 1012 OE1 GLU 267 26.129 13.772 25.444 1.00 42.95
ATOM 1013 OE2 GLU 267 25.449 15.126 23.841 1.00 49.08
ATOM 1014 C GLU 267 23.589 15.643 29.736 1.00 11.52
ATOM 1015 O GLU 267 24.287 14.758 30.254 1.00 11.15
ATOM 1016 N THR 268 22.792 16.465 30.410 1.00 9.46
ATOM 1017 CA THR 268 22.679 16.498 31.857 1.00 9.65
ATOM 1018 CB THR 268 21.712 15.407 32.440 1.00 15.01
ATOM 1019 OG1 THR 268 21.413 15.713 33.815 1.00 18.73
ATOM 1020 CG2 THR 268 22.279 14.019 32.324 1.00 12.06
ATOM 1021 C THR 268 24.050 16.618 32.532 1.00 10.00
ATOM 1022 O THR 268 24.381 15.918 33.488 1.00 10.46
ATOM 1023 N TRP 269 24.840 17.557 32.002 1.00 8.83
ATOM 1024 CA TRP 269 26.164 17.914 32.514 1.00 7.33
ATOM 1025 CB TRP 269 26.014 18.593 33.886 1.00 6.91
ATOM 1026 CG TRP 269 24.941 19.645 33.833 1.00 7.44
ATOM 1027 CD2 TRP 269 24.977 20.858 33.063 1.00 9.25
ATOM 1028 CE2 TRP 269 23.702 21.468 33.182 1.00 9.60
ATOM 1029 CE3 TRP 269 25.963 21.482 32.280 1.00 9.02
ATOM 1030 CD1 TRP 269 23.688 19.578 34.380 1.00 8.91
ATOM 1031 NE1 TRP 269 22.936 20.667 33.990 1.00 9.46
ATOM 1032 CZ2 TRP 269 23.391 22.678 32.542 1.00 10.78
ATOM 1033 CZ3 TRP 269 25.655 22.676 31.648 1.00 8.88
ATOM 1034 CH2 TRP 269 24.384 23.260 31.780 1.00 9.58
ATOM 1035 C TRP 269 27.167 16.784 32.539 1.00 9.24
ATOM 1036 O TRP 269 27.993 16.668 33.447 1.00 9.17
ATOM 1037 N ARG 270 27.130 15.987 31.482 1.00 8.34
ATOM 1038 CA ARG 270 28.034 14.867 31.364 1.00 10.31
ATOM 1039 CB ARG 270 27.237 13.561 31.218 1.00 12.83
ATOM 1040 CG ARG 270 26.506 13.153 32.487 1.00 13.79
ATOM 1041 CD ARG 270 25.929 11.744 32.374 1.00 21.22
ATOM 1042 NE ARG 270 25.323 11.363 33.649 1.00 39.86
ATOM 1043 CZ ARG 270 24.063 10.953 33.798 1.00 53.84
ATOM 1044 NH1 ARG 270 23.261 10.841 32.736 1.00 52.16
ATOM 1045 NH2 ARG 270 23.568 10.778 35.023 1.00 58.09
ATOM 1046 C ARG 270 29.045 14.999 30.223 1.00 13.63
ATOM 1047 O ARG 270 30.025 14.251 30.173 1.00 17.45

ATOM 1048 N THR 271 28.874 15.987 29.356 1.00 10.29
ATOM 1049 CA THR 271 29.799 16.117 28.250 1.00 10.70
ATOM 1050 CB THR 271 29.112 15.726 26.918 1.00 12.98
ATOM 1051 OG1 THR 271 30.104 15.625 25.875 1.00 14.76
ATOM 1052 CG2 THR 271 28.065 16.768 26.533 1.00 11.47
ATOM 1053 C THR 271 30.374 17.510 28.087 1.00 7.92
ATOM 1054 O THR 271 29.717 18.501 28.412 1.00 12.00
ATOM 1055 N GLU 272 31.614 17.571 27.620 1.00 8.88
ATOM 1056 CA GLU 272 32.267 18.841 27.346 1.00 11.22
ATOM 1057 CB GLU 272 33.478 19.069 28.262 1.00 12.02
ATOM 1058 CG GLU 272 34.634 18.058 28.148 1.00 13.79
ATOM 1059 CD GLU 272 35.909 18.622 28.765 1.00 24.86
ATOM 1060 OE1 GLU 272 36.848 18.971 28.013 1.00 26.85
ATOM 1061 OE2 GLU 272 35.958 18.761 30.005 1.00 25.32
ATOM 1062 C GLU 272 32.658 18.909 25.852 1.00 12.64
ATOM 1063 O GLU 272 33.504 19.716 25.453 1.00 14.03
ATOM 1064 N THR 273 32.010 18.087 25.029 1.00 11.26
ATOM 1065 CA THR 273 32.280 18.071 23.588 1.00 12.66
ATOM 1066 CB THR 273 31.516 16.922 22.895 1.00 16.48
ATOM 1067 OG1 THR 273 31.987 16.778 21.551 1.00 32.58
ATOM 1068 CG2 THR 273 30.030 17.194 22.871 1.00 15.77
ATOM 1069 C THR 273 31.886 19.423 22.972 1.00 13.21
ATOM 1070 O THR 273 30.926 20.065 23.441 1.00 13.27
ATOM 1071 N THR 274 32.600 19.860 21.925 1.00 10.07
ATOM 1072 CA THR 274 32.291 21.165 21.326 1.00 10.48
ATOM 1073 CB THR 274 33.375 21.663 20.341 1.00 11.25
ATOM 1074 OG1 THR 274 33.429 20.802 19.198 1.00 11.26
ATOM 1075 CG2 THR 274 34.731 21.714 21.005 1.00 12.70
ATOM 1076 C THR 274 30.948 21.290 20.631 1.00 11.19
ATOM 1077 O THR 274 30.374 22.380 20.588 1.00 13.84
ATOM 1078 N GLY 275 30.461 20.183 20.081 1.00 12.95
ATOM 1079 CA GLY 275 29.195 20.186 19.381 1.00 13.46
ATOM 1080 C GLY 275 27.961 20.216 20.255 1.00 16.29
ATOM 1081 O GLY 275 26.895 20.612 19.788 1.00 22.92
ATOM 1082 N ALA 276 28.066 19.791 21.507 1.00 12.83
ATOM 1083 CA ALA 276 26.894 19.806 22.381 1.00 12.40
ATOM 1084 CB ALA 276 27.033 18.746 23.452 1.00 10.70
ATOM 1085 C ALA 276 26.742 21.191 23.021 1.00 10.43
ATOM 1086 O ALA 276 27.735 21.912 23.164 1.00 10.44
ATOM 1087 N THR 277 25.516 21.558 23.399 1.00 9.22
ATOM 1088 CA THR 277 25.301 22.855 24.029 1.00 9.06
ATOM 1089 CB THR 277 24.491 23.849 23.140 1.00 14.14
ATOM 1090 OG1 THR 277 23.154 23.370 22.969 1.00 21.05
ATOM 1091 CG2 THR 277 25.167 24.048 21.787 1.00 17.07
ATOM 1092 C THR 277 24.606 22.800 25.379 1.00 10.02
ATOM 1093 O THR 277 23.905 21.830 25.720 1.00 10.24
ATOM 1094 N GLY 278 24.784 23.888 26.120 1.00 10.62
ATOM 1095 CA GLY 278 24.158 24.054 27.413 1.00 10.07
ATOM 1096 C GLY 278 23.663 25.485 27.473 1.00 9.01
ATOM 1097 O GLY 278 24.303 26.386 26.923 1.00 10.30
ATOM 1098 N GLN 279 22.519 25.701 28.106 1.00 7.20
ATOM 1099 CA GLN 279 21.982 27.050 28.216 1.00 7.37
ATOM 1100 CB GLN 279 20.487 27.024 28.524 1.00 6.93

ATOM 1101 CG GLN 279 19.724 28.188 27.921 1.00 7.69
ATOM 1102 CD GLN 279 19.459 28.006 26.419 1.00 14.20
ATOM 1103 OE1 GLN 279 20.091 27.189 25.745 1.00 12.46
ATOM 1104 NE2 GLN 279 18.504 28.751 25.906 1.00 13.42
ATOM 1105 C GLN 279 22.773 27.799 29.302 1.00 8.48
ATOM 1106 O GLN 279 22.940 27.313 30.423 1.00 8.67
ATOM 1107 N ALA 280 23.261 28.977 28.949 1.00 7.19
ATOM 1108 CA ALA 280 24.089 29.772 29.838 1.00 7.73
ATOM 1109 CB ALA 280 25.561 29.646 29.434 1.00 9.40
ATOM 1110 C ALA 280 23.663 31.223 29.790 1.00 9.97
ATOM 1111 O ALA 280 22.879 31.618 28.924 1.00 11.40
ATOM 1112 N SER 281 24.165 32.007 30.740 1.00 9.84
ATOM 1113 CA SER 281 23.823 33.413 30.831 1.00 9.93
ATOM 1114 CB SER 281 22.830 33.602 31.969 1.00 8.72
ATOM 1115 OG SER 281 22.456 34.970 32.080 1.00 10.75
ATOM 1116 C SER 281 25.050 34.280 31.096 1.00 13.00
ATOM 1117 O SER 281 25.897 33.935 31.918 1.00 11.02
ATOM 1118 N SER 282 25.108 35.438 30.442 1.00 10.37
ATOM 1119 CA SER 282 26.212 36.346 30.646 1.00 9.96
ATOM 1120 CB SER 282 26.384 37.281 29.455 1.00 11.10
ATOM 1121 OG SER 282 27.539 38.081 29.646 1.00 15.65
ATOM 1122 C SER 282 25.952 37.197 31.865 1.00 10.90
ATOM 1123 O SER 282 24.996 37.957 31.910 1.00 12.82
ATOM 1124 N LEU 283 26.849 37.111 32.829 1.00 11.53
ATOM 1125 CA LEU 283 26.740 37.901 34.035 1.00 14.28
ATOM 1126 CB LEU 283 27.725 37.361 35.070 1.00 19.36
ATOM 1127 CG LEU 283 27.228 37.238 36.502 1.00 28.95
ATOM 1128 CD1 LEU 283 25.814 36.665 36.542 1.00 25.11
ATOM 1129 CD2 LEU 283 28.213 36.355 37.248 1.00 33.05
ATOM 1130 C LEU 283 27.030 39.382 33.724 1.00 16.05
ATOM 1131 O LEU 283 26.673 40.272 34.507 1.00 16.78
ATOM 1132 N LEU 284 27.673 39.646 32.586 1.00 14.06
ATOM 1133 CA LEU 284 27.974 41.018 32.191 1.00 16.31
ATOM 1134 CB LEU 284 28.930 41.058 30.989 1.00 13.83
ATOM 1135 CG LEU 284 30.296 40.405 31.242 1.00 14.35
ATOM 1136 CD1 LEU 284 31.078 40.305 29.965 1.00 16.51
ATOM 1137 CD2 LEU 284 31.062 41.159 32.276 1.00 16.99
ATOM 1138 C LEU 284 26.683 41.778 31.886 1.00 18.57
ATOM 1139 O LEU 284 26.626 42.995 32.054 1.00 22.25
ATOM 1140 N SER 285 25.635 41.062 31.490 1.00 16.42
ATOM 1141 CA SER 285 24.348 41.692 31.194 1.00 18.85
ATOM 1142 CB SER 285 23.585 40.869 30.154 1.00 17.75
ATOM 1143 OG SER 285 23.058 39.678 30.723 1.00 22.16
ATOM 1144 C SER 285 23.480 41.867 32.454 1.00 19.12
ATOM 1145 O SER 285 22.353 42.347 32.367 1.00 22.78
ATOM 1146 N GLY 286 24.002 41.463 33.611 1.00 18.11
ATOM 1147 CA GLY 286 23.262 41.568 34.857 1.00 17.95
ATOM 1148 C GLY 286 22.170 40.528 35.071 1.00 19.04
ATOM 1149 O GLY 286 21.418 40.638 36.034 1.00 20.27
ATOM 1150 N ARG 287 22.129 39.475 34.251 1.00 15.86
ATOM 1151 CA ARG 287 21.088 38.447 34.374 1.00 12.80
ATOM 1152 CB ARG 287 20.240 38.400 33.097 1.00 12.46
ATOM 1153 CG ARG 287 19.505 39.678 32.804 1.00 14.92

ATOM 1154 CD ARG 287 18.968 39.685 31.378 1.00 25.50
ATOM 1155 NE ARG 287 20.036 39.683 30.378 1.00 25.57
ATOM 1156 CZ ARG 287 19.847 39.560 29.066 1.00 27.33
ATOM 1157 NH1 ARG 287 18.625 39.430 28.571 1.00 25.30
ATOM 1158 NH2 ARG 287 20.889 39.558 28.246 1.00 25.11
ATOM 1159 C ARG 287 21.663 37.056 34.613 1.00 12.17
ATOM 1160 O ARG 287 22.758 36.743 34.142 1.00 13.69
ATOM 1161 N LEU 288 20.893 36.213 35.300 1.00 10.50
ATOM 1162 CA LEU 288 21.293 34.830 35.585 1.00 12.07
ATOM 1163 CB LEU 288 20.855 34.420 36.993 1.00 11.10
ATOM 1164 CG LEU 288 21.497 35.098 38.187 1.00 13.11
ATOM 1165 CD1 LEU 288 20.843 34.559 39.460 1.00 14.89
ATOM 1166 CD2 LEU 288 22.974 34.818 38.182 1.00 16.30
ATOM 1167 C LEU 288 20.669 33.821 34.633 1.00 11.63
ATOM 1168 O LEU 288 21.181 32.719 34.493 1.00 11.03
ATOM 1169 N LEU 289 19.574 34.201 33.975 1.00 10.91
ATOM 1170 CA LEU 289 18.843 33.273 33.113 1.00 11.22
ATOM 1171 CB LEU 289 17.479 32.923 33.751 1.00 12.01
ATOM 1172 CG LEU 289 17.476 32.243 35.134 1.00 12.63
ATOM 1173 CD1 LEU 289 16.068 32.236 35.706 1.00 12.30
ATOM 1174 CD2 LEU 289 18.024 30.808 35.019 1.00 12.35
ATOM 1175 C LEU 289 18.663 33.681 31.648 1.00 11.78
ATOM 1176 O LEU 289 17.668 33.342 31.018 1.00 12.35
ATOM 1177 N GLU 290 19.634 34.409 31.116 1.00 11.86
ATOM 1178 CA GLU 290 19.635 34.789 29.714 1.00 13.35
ATOM 1179 CB GLU 290 20.924 35.555 29.430 1.00 17.02
ATOM 1180 CG GLU 290 21.092 36.101 28.037 1.00 40.20
ATOM 1181 CD GLU 290 22.326 36.986 27.919 1.00 49.50
ATOM 1182 OE1 GLU 290 23.203 36.932 28.803 1.00 39.91
ATOM 1183 OE2 GLU 290 22.438 37.741 26.930 1.00 62.69
ATOM 1184 C GLU 290 19.593 33.460 28.944 1.00 14.01
ATOM 1185 O GLU 290 20.058 32.421 29.435 1.00 14.47
ATOM 1186 N GLN 291 19.030 33.475 27.752 1.00 13.28
ATOM 1187 CA GLN 291 18.896 32.249 26.974 1.00 13.39
ATOM 1188 CB GLN 291 17.476 32.180 26.437 1.00 12.23
ATOM 1189 CG GLN 291 16.468 32.161 27.568 1.00 13.53
ATOM 1190 CD GLN 291 16.552 30.881 28.348 1.00 12.24
ATOM 1191 OE1 GLN 291 16.370 29.816 27.786 1.00 13.87
ATOM 1192 NE2 GLN 291 16.867 30.971 29.631 1.00 10.73
ATOM 1193 C GLN 291 19.910 32.045 25.858 1.00 15.73
ATOM 1194 O GLN 291 19.572 32.170 24.676 1.00 21.34
ATOM 1195 N LYS 292 21.154 31.763 26.237 1.00 13.25
ATOM 1196 CA LYS 292 22.221 31.524 25.283 1.00 13.64
ATOM 1197 CB LYS 292 23.471 32.325 25.656 1.00 15.76
ATOM 1198 CG LYS 292 23.494 33.772 25.221 0.00 14.29
ATOM 1199 CD LYS 292 24.929 34.283 25.262 0.00 13.82
ATOM 1200 CE LYS 292 25.038 35.744 24.875 0.00 13.29
ATOM 1201 NZ LYS 292 24.457 36.626 25.903 0.00 12.93
ATOM 1202 C LYS 292 22.600 30.048 25.236 1.00 16.34
ATOM 1203 O LYS 292 22.889 29.446 26.266 1.00 16.97
ATOM 1204 N ALA 293 22.594 29.460 24.041 1.00 15.29
ATOM 1205 CA ALA 293 22.998 28.066 23.877 1.00 15.09
ATOM 1206 CB ALA 293 22.305 27.458 22.691 1.00 17.19

ATOM 1207 C ALA 293 24.501 28.141 23.627 1.00 18.98
ATOM 1208 O ALA 293 24.930 28.682 22.594 1.00 22.49
ATOM 1209 N ALA 294 25.298 27.698 24.602 1.00 15.43
ATOM 1210 CA ALA 294 26.763 27.748 24.498 1.00 13.78
ATOM 1211 CB ALA 294 27.353 28.469 25.729 1.00 10.17
ATOM 1212 C ALA 294 27.390 26.362 24.370 1.00 12.39
ATOM 1213 O ALA 294 26.869 25.389 24.914 1.00 11.83
ATOM 1214 N SER 295 28.494 26.266 23.636 1.00 9.52
ATOM 1215 CA SER 295 29.185 24.989 23.493 1.00 10.89
ATOM 1216 CB SER 295 30.450 25.148 22.646 1.00 10.02
ATOM 1217 OG SER 295 31.295 24.013 22.720 1.00 10.54
ATOM 1218 C SER 295 29.594 24.502 24.884 1.00 9.64
ATOM 1219 O SER 295 30.166 25.262 25.683 1.00 9.24
ATOM 1220 N CYS 296 29.386 23.212 25.112 1.00 8.90
ATOM 1221 CA CYS 296 29.709 22.581 26.380 1.00 10.24
ATOM 1222 C CYS 296 31.188 22.555 26.696 1.00 9.59
ATOM 1223 O CYS 296 31.588 22.266 27.829 1.00 9.50
ATOM 1224 CB CYS 296 29.128 21.175 26.412 1.00 8.51
ATOM 1225 SG CYS 296 27.315 21.214 26.322 1.00 10.52
ATOM 1226 N HIS 297 32.012 22.842 25.698 1.00 8.62
ATOM 1227 CA HIS 297 33.440 22.851 25.908 1.00 9.50
ATOM 1228 CB HIS 297 34.166 22.677 24.576 1.00 9.64
ATOM 1229 CG HIS 297 35.613 22.358 24.735 1.00 9.70
ATOM 1230 CD2 HIS 297 36.233 21.199 25.039 1.00 15.57
ATOM 1231 ND1 HIS 297 36.598 23.310 24.621 1.00 14.69
ATOM 1232 CE1 HIS 297 37.774 22.750 24.848 1.00 19.73
ATOM 1233 NE2 HIS 297 37.578 21.468 25.103 1.00 23.00
ATOM 1234 C HIS 297 33.935 24.116 26.667 1.00 9.12
ATOM 1235 O HIS 297 35.090 24.185 27.104 1.00 11.63
ATOM 1236 N ASN 298 33.069 25.119 26.789 1.00 8.35
ATOM 1237 CA ASN 298 33.405 26.337 27.522 1.00 8.97
ATOM 1238 CB ASN 298 32.316 27.395 27.299 1.00 8.79
ATOM 1239 CG ASN 298 32.437 28.090 25.952 1.00 8.51
ATOM 1240 OD1 ASN 298 33.344 28.879 25.735 1.00 11.82
ATOM 1241 ND2 ASN 298 31.508 27.812 25.062 1.00 11.49
ATOM 1242 C ASN 298 33.490 26.063 29.037 1.00 10.39
ATOM 1243 O ASN 298 32.731 25.244 29.571 1.00 11.28
ATOM 1244 N SER 299 34.384 26.782 29.711 1.00 10.29
ATOM 1245 CA SER 299 34.559 26.686 31.166 1.00 10.47
ATOM 1246 CB SER 299 36.045 26.616 31.559 1.00 14.97
ATOM 1247 OG SER 299 36.576 25.322 31.310 1.00 28.18
ATOM 1248 C SER 299 33.915 27.945 31.732 1.00 10.29
ATOM 1249 O SER 299 34.470 29.039 31.604 1.00 11.16
ATOM 1250 N TYR 300 32.726 27.772 32.313 1.00 9.29
ATOM 1251 CA TYR 300 31.918 28.856 32.859 1.00 8.49
ATOM 1252 CB TYR 300 30.518 28.814 32.206 1.00 7.10
ATOM 1253 CG TYR 300 30.426 29.295 30.764 1.00 7.59
ATOM 1254 CD1 TYR 300 31.445 30.062 30.183 1.00 10.11
ATOM 1255 CE1 TYR 300 31.326 30.561 28.876 1.00 9.19
ATOM 1256 CD2 TYR 300 29.296 29.016 30.004 1.00 8.62
ATOM 1257 CE2 TYR 300 29.166 29.499 28.714 1.00 11.31
ATOM 1258 CZ TYR 300 30.184 30.269 28.156 1.00 12.94
ATOM 1259 OH TYR 300 30.041 30.731 26.871 1.00 16.38

ATOM 1260 C TYR 300 31.742 28.745 34.385 1.00 9.73
ATOM 1261 O TYR 300 32.102 27.744 35.013 1.00 8.08
ATOM 1262 N ILE 301 31.188 29.808 34.947 1.00 7.28
ATOM 1263 CA ILE 301 30.888 29.902 36.358 1.00 7.35
ATOM 1264 CB ILE 301 30.413 31.337 36.707 1.00 7.56
ATOM 1265 CG2 ILE 301 29.979 31.432 38.185 1.00 9.38
ATOM 1266 CG1 ILE 301 31.522 32.345 36.383 1.00 10.75
ATOM 1267 CD1 ILE 301 31.026 33.774 36.266 1.00 11.79
ATOM 1268 C ILE 301 29.724 28.955 36.671 1.00 7.08
ATOM 1269 O ILE 301 28.794 28.801 35.873 1.00 7.60
ATOM 1270 N VAL 302 29.804 28.300 37.821 1.00 6.56
ATOM 1271 CA VAL 302 28.729 27.441 38.274 1.00 6.59
ATOM 1272 CB VAL 302 29.159 25.960 38.347 1.00 7.08
ATOM 1273 CG1 VAL 302 28.029 25.130 38.948 1.00 9.28
ATOM 1274 CG2 VAL 302 29.511 25.448 36.931 1.00 8.65
ATOM 1275 C VAL 302 28.363 27.949 39.659 1.00 7.34
ATOM 1276 O VAL 302 29.260 28.166 40.504 1.00 9.31
ATOM 1277 N LEU 303 27.065 28.165 39.878 1.00 5.98
ATOM 1278 CA LEU 303 26.566 28.643 41.168 1.00 6.62
ATOM 1279 CB LEU 303 25.520 29.748 40.951 1.00 5.91
ATOM 1280 CG LEU 303 25.974 30.946 40.105 1.00 5.79
ATOM 1281 CD1 LEU 303 24.809 31.914 39.936 1.00 9.29
ATOM 1282 CD2 LEU 303 27.168 31.626 40.751 1.00 8.55
ATOM 1283 C LEU 303 25.934 27.525 42.012 1.00 6.94
ATOM 1284 O LEU 303 25.483 26.493 41.483 1.00 7.50
ATOM 1285 N CYS 304 25.895 27.758 43.323 1.00 5.58
ATOM 1286 CA CYS 304 25.292 26.843 44.290 1.00 6.15
ATOM 1287 C CYS 304 24.297 27.684 45.079 1.00 7.15
ATOM 1288 O CYS 304 24.600 28.826 45.461 1.00 8.17
ATOM 1289 CB CYS 304 26.329 26.294 45.275 1.00 7.42
ATOM 1290 SG CYS 304 27.741 25.452 44.518 1.00 7.96
ATOM 1291 N ILE 305 23.114 27.132 45.286 1.00 6.12
ATOM 1292 CA ILE 305 22.064 27.815 46.020 1.00 7.49
ATOM 1293 CB ILE 305 20.779 28.031 45.115 1.00 7.52
ATOM 1294 CG2 ILE 305 20.332 26.704 44.452 1.00 9.27
ATOM 1295 CG1 ILE 305 19.628 28.676 45.913 1.00 10.13
ATOM 1296 CD1 ILE 305 19.824 30.143 46.247 1.00 11.16
ATOM 1297 C ILE 305 21.698 27.046 47.293 1.00 10.06
ATOM 1298 O ILE 305 21.602 25.813 47.287 1.00 9.16
ATOM 1299 N GLU 306 21.565 27.784 48.393 1.00 7.92
ATOM 1300 CA GLU 306 21.152 27.232 49.690 1.00 10.18
ATOM 1301 CB GLU 306 21.306 28.317 50.739 1.00 10.07
ATOM 1302 CG GLU 306 21.335 27.819 52.146 1.00 13.04
ATOM 1303 CD GLU 306 21.750 28.908 53.124 1.00 20.14
ATOM 1304 OE1 GLU 306 21.900 30.077 52.706 1.00 10.57
ATOM 1305 OE2 GLU 306 21.934 28.603 54.320 1.00 24.88
ATOM 1306 C GLU 306 19.681 26.872 49.478 1.00 9.73
ATOM 1307 O GLU 306 18.873 27.739 49.139 1.00 11.98
ATOM 1308 N ASN 307 19.322 25.606 49.677 1.00 10.68
ATOM 1309 CA ASN 307 17.960 25.186 49.355 1.00 13.13
ATOM 1310 CB ASN 307 17.937 23.747 48.816 1.00 17.30
ATOM 1311 CG ASN 307 18.054 22.697 49.904 1.00 33.21
ATOM 1312 OD1 ASN 307 17.751 21.521 49.665 1.00 42.13

ATOM 1313 ND2 ASN 307 18.483 23.099 51.104 1.00 34.89
ATOM 1314 C ASN 307 16.836 25.438 50.343 1.00 13.53
ATOM 1315 O ASN 307 15.665 25.234 50.028 1.00 14.73
ATOM 1316 N SER 308 17.199 25.938 51.513 1.00 15.33
ATOM 1317 CA SER 308 16.228 26.268 52.540 1.00 17.72
ATOM 1318 CB SER 308 15.658 24.992 53.155 1.00 21.56
ATOM 1319 OG SER 308 16.711 24.160 53.619 1.00 25.37
ATOM 1320 C SER 308 16.937 27.062 53.621 1.00 16.82
ATOM 1321 O SER 308 18.156 26.967 53.754 1.00 17.25
ATOM 1322 N PHE 309 16.193 27.911 54.318 1.00 19.67
ATOM 1323 CA PHE 309 16.754 28.674 55.429 1.00 21.81
ATOM 1324 CB PHE 309 16.009 30.000 55.650 1.00 19.28
ATOM 1325 CG PHE 309 16.483 30.765 56.855 0.00 20.57
ATOM 1326 CD1 PHE 309 17.742 31.357 56.868 0.00 20.77
ATOM 1327 CD2 PHE 309 15.676 30.887 57.983 0.00 20.76
ATOM 1328 CE1 PHE 309 18.193 32.058 57.987 0.00 21.12
ATOM 1329 CE2 PHE 309 16.116 31.586 59.108 0.00 21.12
ATOM 1330 CZ PHE 309 17.379 32.173 59.109 0.00 21.23
ATOM 1331 C PHE 309 16.563 27.762 56.635 1.00 22.35
ATOM 1332 O PHE 309 17.541 27.533 57.353 1.00 26.83
ATOM 1333 OT PHE 309 15.440 27.254 56.828 1.00 26.72
ATOM 1334 OW WAT 401 35.042 31.373 33.454 1.00 14.12
ATOM 1335 OW WAT 402 28.187 34.855 46.584 1.00 7.88
ATOM 1336 OW WAT 403 35.662 26.376 49.640 1.00 11.26
ATOM 1337 OW WAT 404 25.161 27.442 37.820 1.00 10.17
ATOM 1338 OW WAT 405 32.569 28.701 39.266 1.00 8.09
ATOM 1339 OW WAT 406 23.115 17.509 48.067 1.00 15.06
ATOM 1340 OW WAT 407 23.144 14.278 35.669 1.00 17.19
ATOM 1341 OW WAT 408 12.544 33.294 48.204 1.00 12.28
ATOM 1342 OW WAT 409 24.735 12.279 37.713 1.00 21.94
ATOM 1343 OW WAT 410 31.247 14.687 32.770 1.00 19.39
ATOM 1344 OW WAT 411 21.080 20.697 41.768 1.00 13.46
ATOM 1345 OW WAT 412 21.911 18.669 26.262 1.00 16.11
ATOM 1346 OW WAT 413 12.899 34.774 34.572 1.00 13.93
ATOM 1347 OW WAT 414 15.656 21.976 25.008 1.00 20.91
ATOM 1348 OW WAT 415 29.212 28.531 22.036 1.00 16.40
ATOM 1349 OW WAT 416 24.593 28.373 55.308 1.00 34.65
ATOM 1350 OW WAT 417 35.097 24.019 41.496 1.00 22.94
ATOM 1351 OW WAT 418 18.566 14.927 37.495 1.00 18.73
ATOM 1352 OW WAT 419 35.149 17.242 31.998 1.00 23.10
ATOM 1353 OW WAT 420 20.849 31.117 55.292 1.00 21.98
ATOM 1354 OW WAT 421 30.294 39.756 40.658 1.00 20.87
ATOM 1355 OW WAT 422 11.858 19.238 39.364 1.00 30.37
ATOM 1356 OW WAT 423 13.182 20.311 28.140 1.00 20.79
ATOM 1357 OW WAT 424 20.499 46.290 51.202 1.00 15.88
ATOM 1358 OW WAT 425 14.486 29.276 25.815 1.00 30.27
ATOM 1359 OW WAT 426 20.437 9.743 35.300 1.00 57.70
ATOM 1360 OW WAT 427 8.107 23.588 51.829 1.00 30.09
ATOM 1361 OW WAT 428 26.082 42.690 45.786 1.00 21.81
ATOM 1362 OW WAT 429 31.932 22.876 57.878 1.00 32.40
ATOM 1363 OW WAT 430 28.484 39.973 38.870 1.00 58.83
ATOM 1364 OW WAT 431 19.349 19.830 39.454 1.00 21.54
ATOM 1365 OW WAT 432 25.178 20.516 50.622 1.00 25.50

ATOM	1366	OW	WAT	433	35.002	19.983	52.334	1.00	19.82
ATOM	1367	OW	WAT	434	34.135	43.191	44.812	1.00	32.07
ATOM	1368	OW	WAT	435	27.063	23.208	54.289	1.00	23.70
ATOM	1369	OW	WAT	436	34.312	17.824	19.412	1.00	39.43
ATOM	1370	OW	WAT	437	20.753	13.370	41.155	1.00	28.09
ATOM	1371	OW	WAT	438	19.252	35.279	59.477	1.00	29.78
ATOM	1372	OW	WAT	439	35.323	21.057	33.845	1.00	26.66
ATOM	1373	OW	WAT	440	21.925	16.767	45.856	1.00	27.17
ATOM	1374	OW	WAT	441	32.382	17.266	39.169	1.00	28.79
ATOM	1375	OW	WAT	442	15.598	41.632	31.052	1.00	27.73
ATOM	1376	OW	WAT	443	29.982	36.780	29.435	1.00	33.39
ATOM	1377	OW	WAT	444	31.371	31.251	61.561	1.00	38.29
ATOM	1378	OW	WAT	445	19.759	24.735	53.771	1.00	36.44
ATOM	1379	OW	WAT	446	22.480	15.079	42.820	1.00	17.58
ATOM	1380	OW	WAT	447	31.988	43.715	40.911	1.00	32.48
ATOM	1381	OW	WAT	448	17.935	35.854	26.456	1.00	28.58
ATOM	1382	OW	WAT	449	39.435	11.740	46.219	1.00	55.63
ATOM	1383	OW	WAT	450	16.672	41.095	41.485	1.00	31.86
ATOM	1384	OW	WAT	451	21.716	44.110	44.322	1.00	34.21
ATOM	1385	OW	WAT	452	18.308	15.003	40.442	1.00	46.38
ATOM	1386	OW	WAT	453	16.863	20.586	46.633	1.00	33.96
ATOM	1387	OW	WAT	454	31.944	31.457	24.450	1.00	42.18
ATOM	1388	OW	WAT	455	33.475	15.082	27.168	1.00	29.91
ATOM	1389	OW	WAT	456	36.543	15.370	34.224	1.00	60.74
ATOM	1390	OW	WAT	457	29.506	42.389	39.975	1.00	50.14
ATOM	1391	OW	WAT	458	20.388	16.126	25.860	1.00	53.32
ATOM	1392	OW	WAT	459	40.036	27.768	47.622	1.00	39.85
ATOM	1393	OW	WAT	460	32.383	15.687	41.430	1.00	39.50
ATOM	1394	OW	WAT	461	24.106	44.984	36.684	1.00	69.51
ATOM	1395	OW	WAT	462	22.963	42.283	26.675	1.00	42.87
ATOM	1396	OW	WAT	463	8.582	32.282	51.088	1.00	27.98
ATOM	1397	OW	WAT	464	23.257	19.528	23.889	1.00	34.76
ATOM	1398	OW	WAT	465	21.735	11.857	38.555	1.00	25.60
ATOM	1399	OW	WAT	466	27.314	36.489	57.830	1.00	58.08
ATOM	1400	OW	WAT	467	40.667	22.670	25.260	1.00	47.16
ATOM	1401	OW	WAT	468	10.401	39.140	49.837	1.00	41.30
ATOM	1402	OW	WAT	469	37.248	23.884	49.023	1.00	29.62
ATOM	1403	OW	WAT	470	21.277	40.716	54.364	1.00	33.13
ATOM	1404	OW	WAT	471	20.847	42.289	42.598	1.00	41.23
ATOM	1405	OW	WAT	472	33.078	36.978	29.346	1.00	29.31
ATOM	1406	OW	WAT	473	35.934	28.368	27.882	1.00	60.80
ATOM	1407	OW	WAT	474	38.008	24.709	46.253	1.00	34.90
ATOM	1408	OW	WAT	475	27.705	21.292	52.433	1.00	33.44
ATOM	1409	OW	WAT	476	37.983	27.433	50.682	1.00	30.01
ATOM	1410	OW	WAT	477	40.276	29.674	40.928	1.00	41.29
ATOM	1411	OW	WAT	478	39.094	29.615	52.097	1.00	30.12
ATOM	1412	OW	WAT	479	31.439	33.313	26.658	1.00	42.81
ATOM	1413	OW	WAT	480	10.829	39.751	38.732	1.00	44.07
ATOM	1414	OW	WAT	481	14.656	39.402	38.495	1.00	33.96
ATOM	1415	OW	WAT	482	34.006	14.898	31.399	1.00	51.26
ATOM	1416	OW	WAT	483	20.382	13.189	36.365	1.00	44.95

What is claimed is:

1. A method of identifying a compound having atomic coordinates with non-trivial similarity to selected coordinates of atoms of a mammalian endostatin, comprising:

a) providing a library of atomic coordinates of compounds in a library of candidate compounds; and

b) comparing the library atomic coordinates to the selected coordinates of a mammalian endostatin; and

c) selecting from the library at least one candidate compound on the basis of selection criteria which include similarities between the atomic coordinates of the selected candidate compound and the atomic coordinates of the mammalian endostatin.

2. The method of claim 1 in which the coordinates of the mammalian endostatin comprise at least one pair of coordinates of Appendix A.

3. The method of claim 1 or claim 2 in which the mammalian endostatin is human endostatin.

4. The method of claim 2 in which the coordinates of mammalian endostatin include coordinates of atoms in a large basic structure area defining a heparin binding site.

5. The method of claim 1 in which coordinates of endostatin are stored in a computer-readable medium, and compared to coordinates of candidate compounds also stored in a computer-readable medium.

6. The method of claim 1 or claim 5 in which at least one of the selected endostatin coordinates represents a coordinate of an atom involved in heparin binding.

7. The method of claim 1 or claim 5 in which at least one of the selected endostatin coordinates represents an atom of at least one of the following amino acid residues: Arg155; Arg158; Arg169; Arg 178; Arg184; Arg 193; Arg 194; Arg197; Arg259; and Arg270 of mouse endostatin.

8. The methdo of claim 1 or claim 5 in which at least one of the selected endostatin coordinates represents an atom of at least one of the following amino acid residues: Arg154, Arg157, Arg168, Arg177, Arg183, Arg192, Arg193, Arg 196, Arg258, Arg 259, and Arg 269 of human endostatin.

9. The method of claim 1 in which at least one of the selected endostatin coordinates represents an atom of an amino acid involved in receptor binding.

10. The method of claim 1 in which at least one of the selected endostatin coordinates represents an atom of an amino acid residue necessary for proteolytic cleavage.

11. The method of claim 1 in which at least one of the selected endostatin coordinates represents an atom of an amino acid residue exposed on α-helix A.

12. The method of claim 1 in which at least one of the selected endostatin coordinates represents an atom of Phe162 or Phe165 of mouse endostatin.

13. The method of claim 1 in which at least one of the selected endostatin coordinates represents an atom of Phe161 or Phe164 of human endostatin.

14. The method of claim 1 in which at least one of the selected endostatin coordinates represents an atom of an amino acid residue involved in the endostatin fold related to the oligosaccharide binding site of E-selectin.

15. The method of claim 1 in which at least one of the selected endostatin coordinates represents an atom of one of the following amino acid residues: Glu267; Leu 284; Lys292; His297; Asn298; Tyr300 of mouse endostatin.

16. The method of claim 1 in which at least one of the selected endostatin coordinates represents an atom of one of the following amino acid residues: Glu266, Leu283, Ser291, His296, His297, and Tyr299 of human endostatin.

17. An anti-angiogenic fragment of endostatin comprising a domain selected from the group consisting of a heparin binding domain, a receptor binding domain, and exposed on α-helix A domain, and a CRD domain.

18. A method of treating undesired angiogenesis by administering to a patient an anti-angiogenic amount of the fragment of claim 14 or of a compound identified by the method of claim 1.

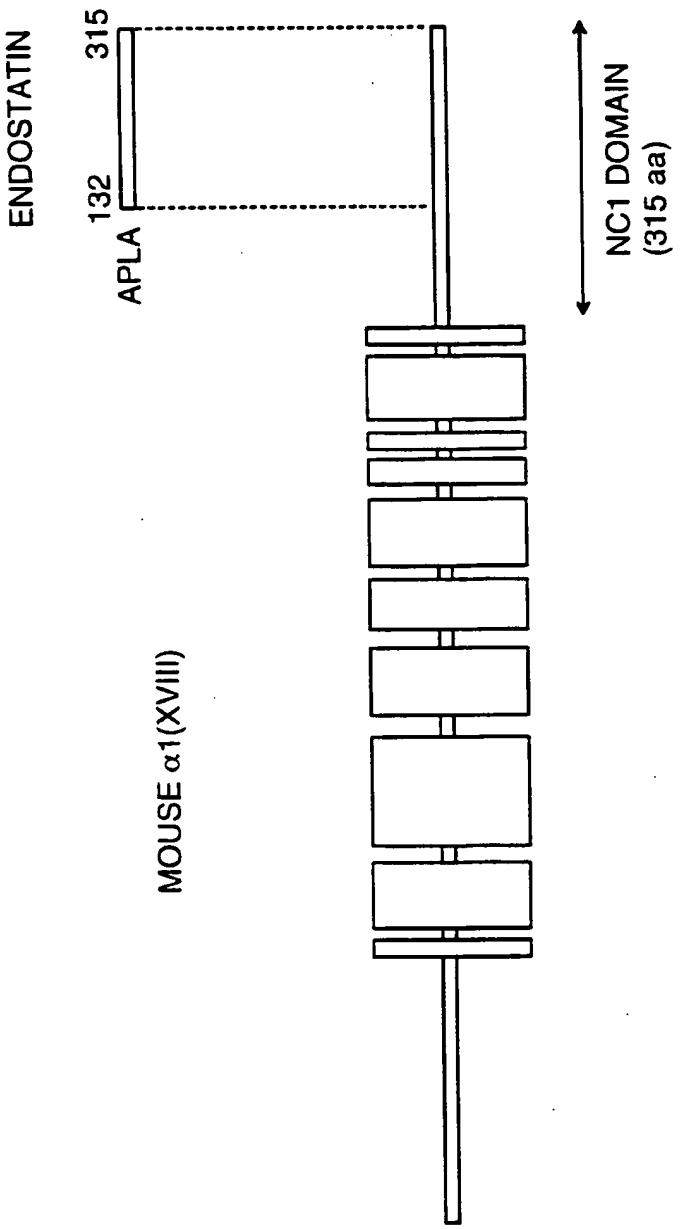


FIG. 1

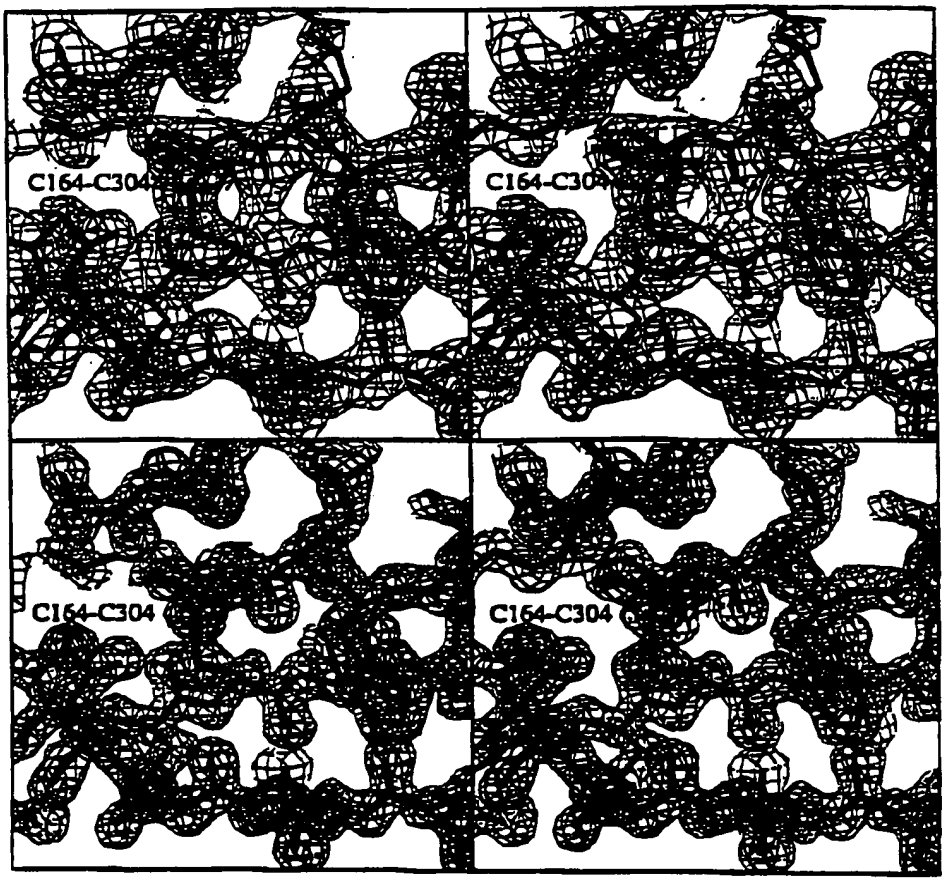


FIG. 2

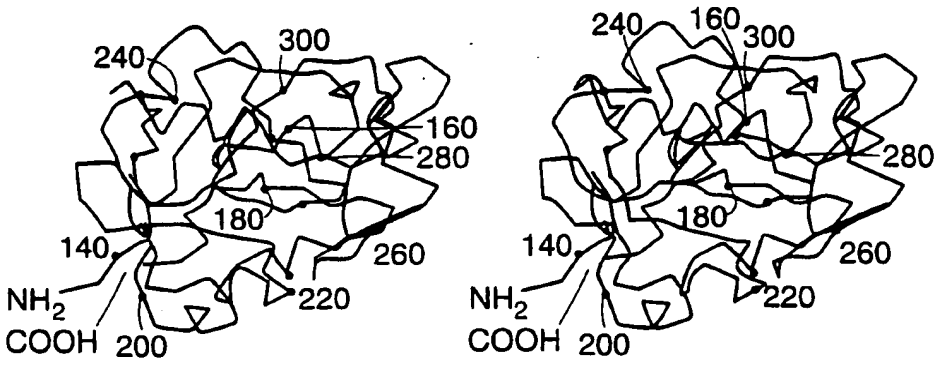

240
300
160
280
180
140
260
NH2
220
COOH
200
240
160
300
280
180
140
260
NH2
220
COOH
200

FIG. 3A

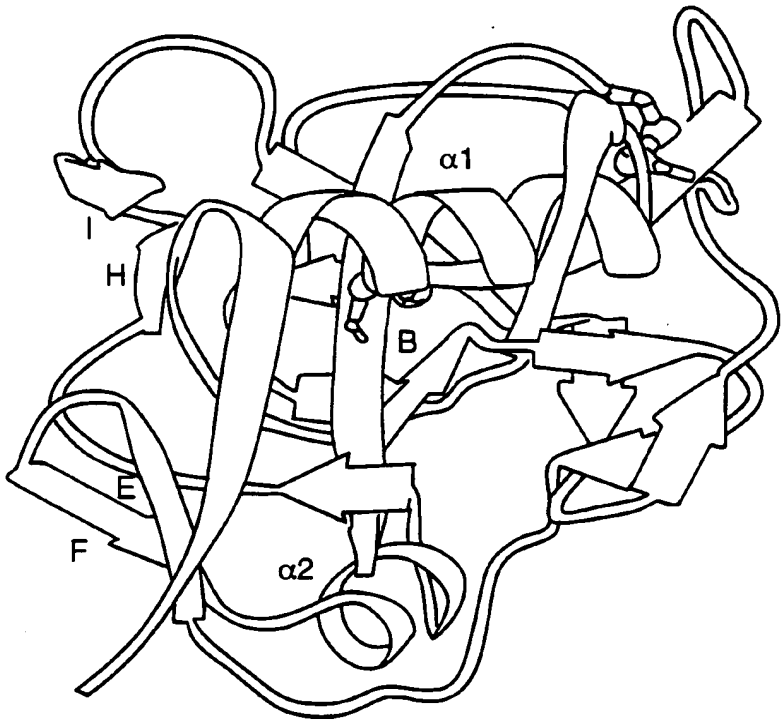

α1
I
H
B
E
F
α2

FIG. 3B

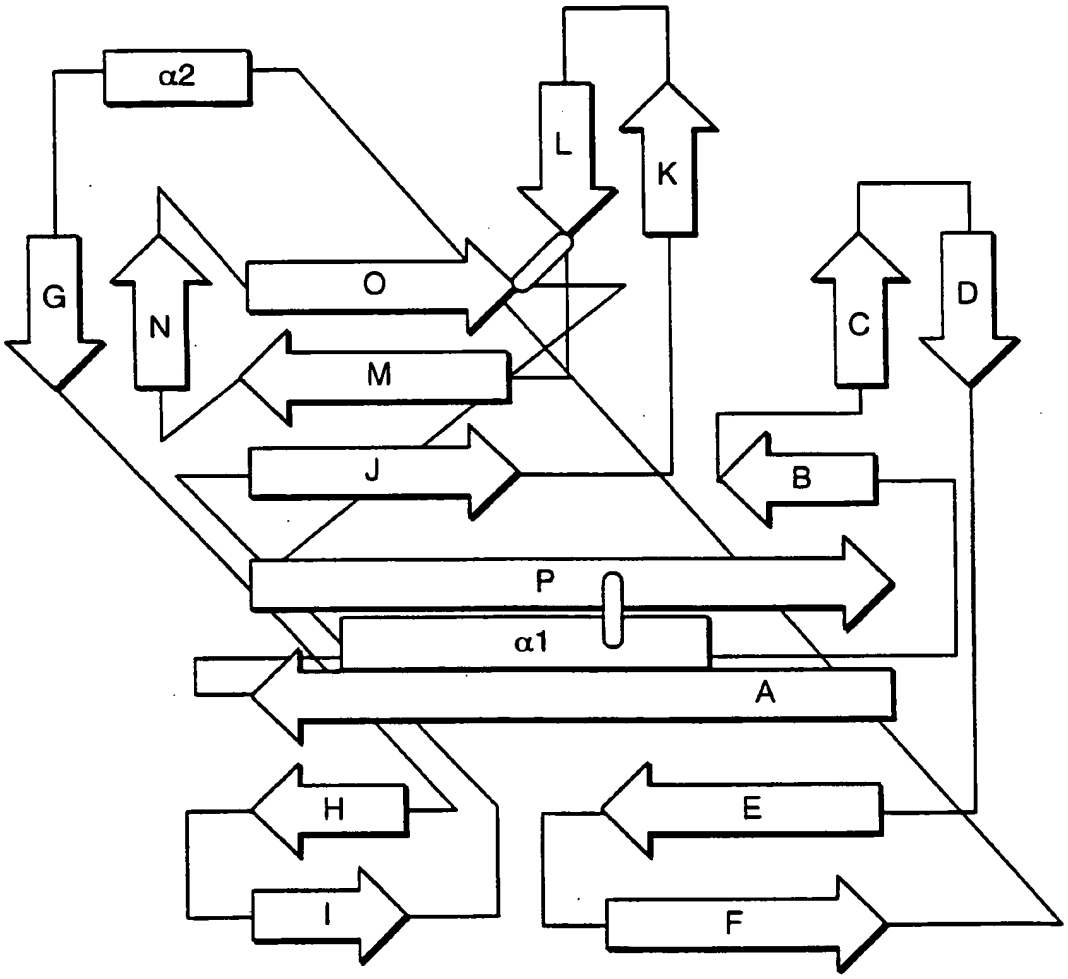


FIG. 3C

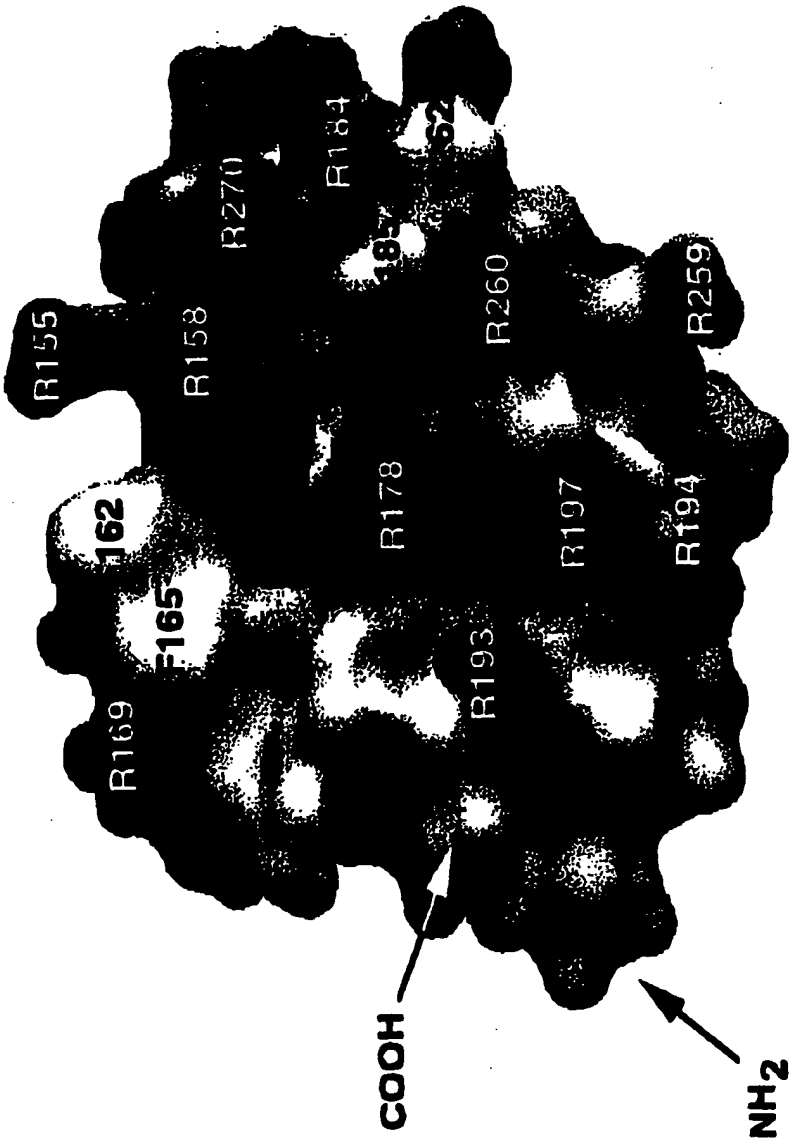

R155
R158
R270
R184
R260
R259
R178
R197
R194
162
F165
R169
R193
COOH
NH2

FIG. 4A

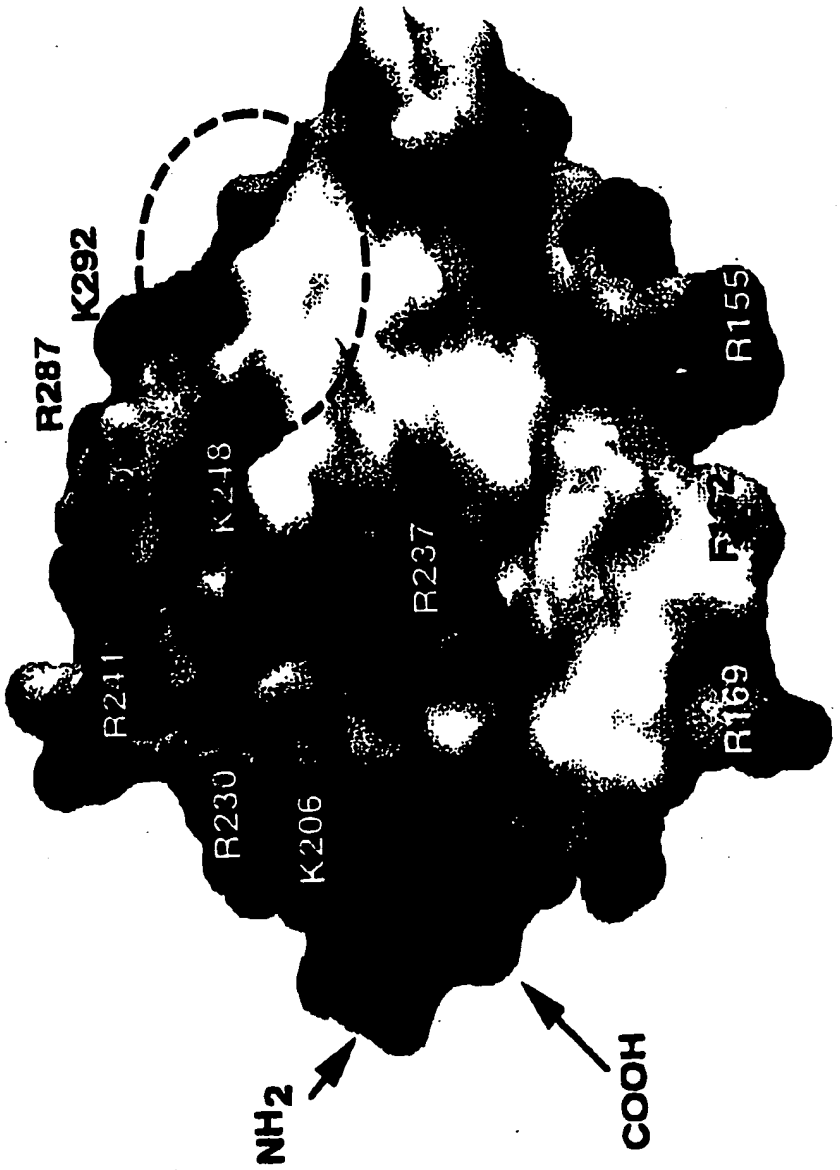
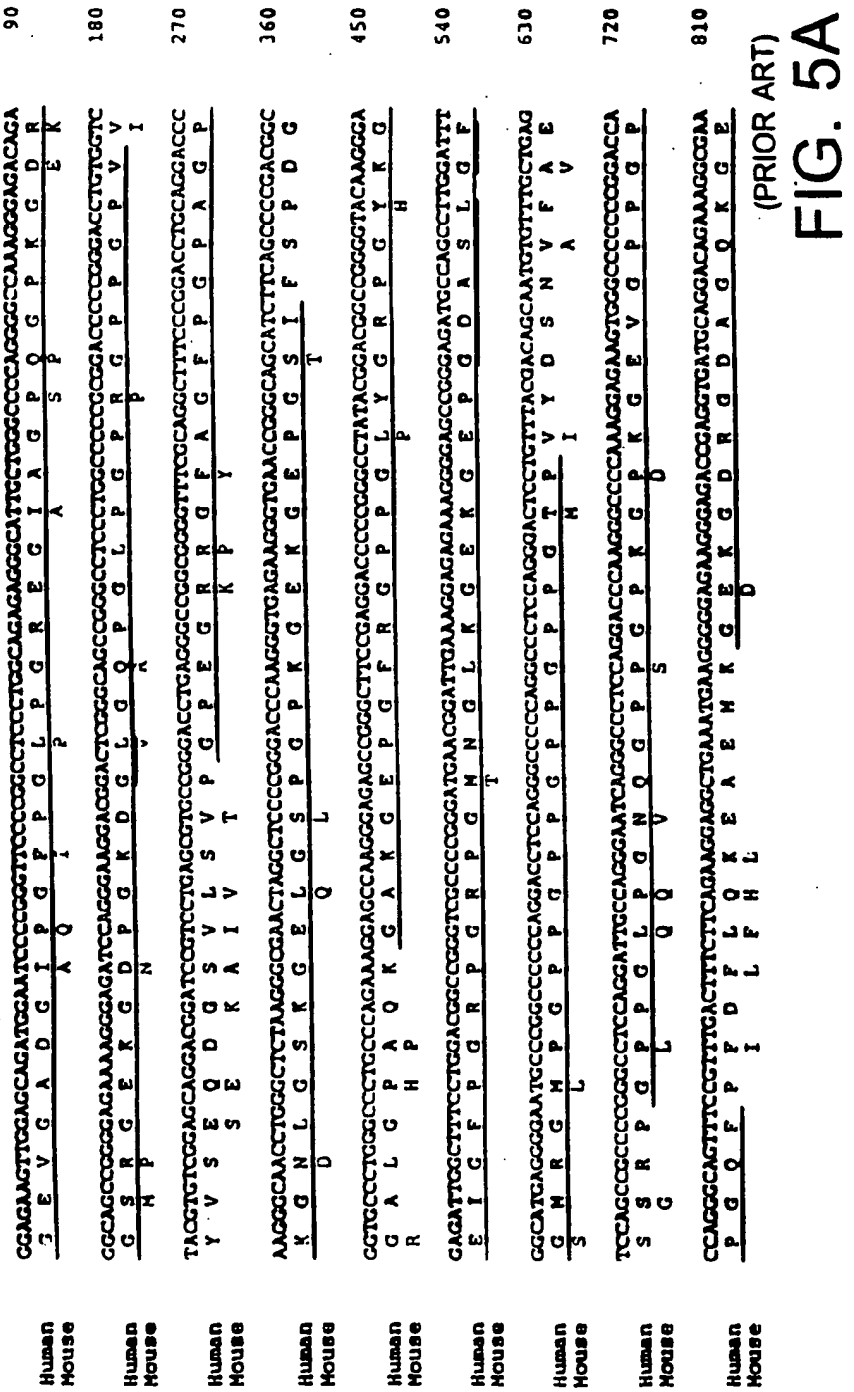
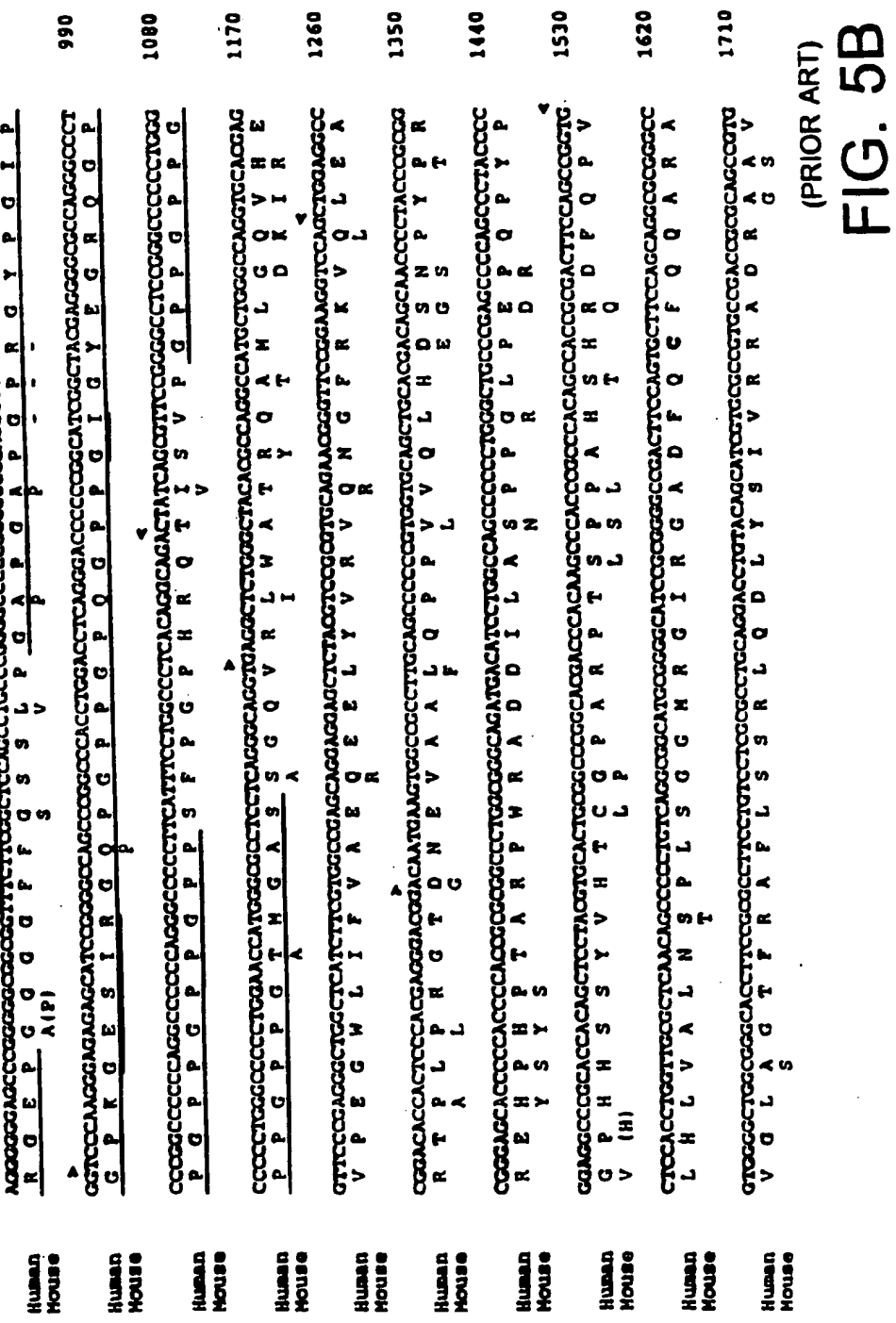


FIG. 4B



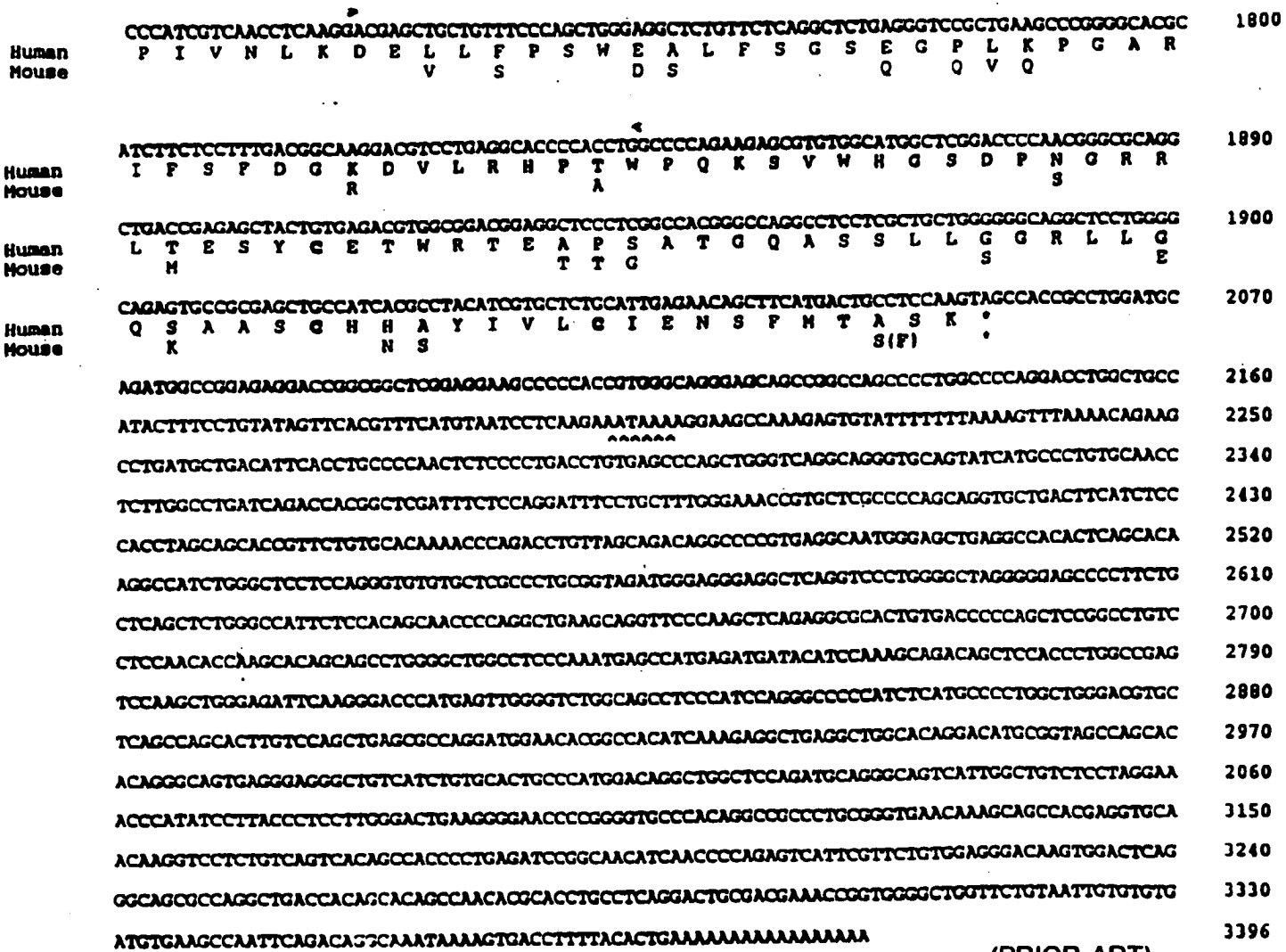
(PRIOR ART)

FIG. 5A



(PRIOR ART)

FIG. 5B



(PRIOR ART)

FIG. 5C

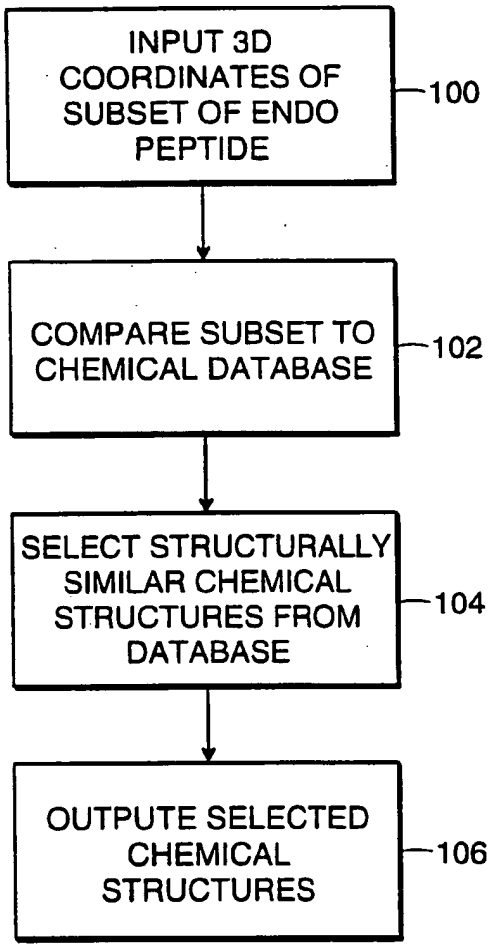

INPUT 3D COORDINATES OF SUBSET OF ENDO PEPTIDE
100
COMPARE SUBSET TO CHEMICAL DATABASE
102
SELECT STRUCTURALLY SIMILAR CHEMICAL STRUCTURES FROM DATABASE
104
OUTPUTE SELECTED CHEMICAL STRUCTURES
106

FIG. 6

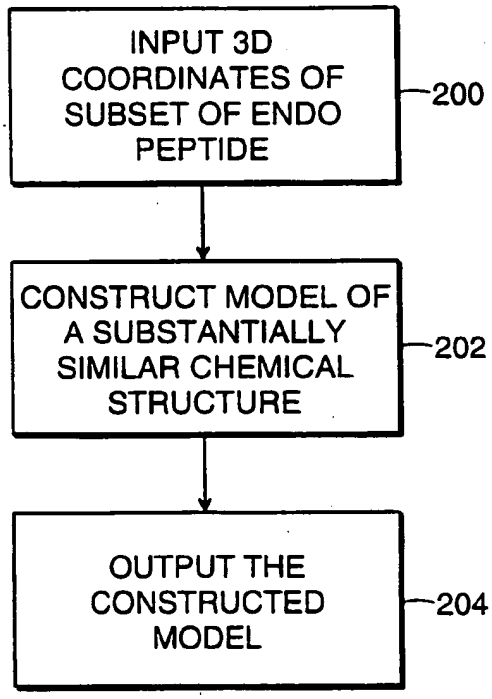

INPUT 3D COORDINATES OF SUBSET OF ENDO PEPTIDE
200
CONSTRUCT MODEL OF A SUBSTANTIALLY SIMILAR CHEMICAL STRUCTURE
202
OUTPUT THE CONSTRUCTED MODEL
204

FIG. 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/26783

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : G06G 7/48; C07K 1/00, 14/00, 16/00, 17/00
US CL : 364/578; 530/300, 350, 356; 514/2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 364/578; 530/300, 350, 356; 514/2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS Dialog WEST (Derwent, USPAT, JPOABS EPOABS)
endostatin, x-ray, crystal structure, atomic coordiates

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DING et al. Zinc-dependent dimers observed in crystals of human endostatin. Proc. Natl. Acad. Sci. 01 September 1998, Vol. 95, No. 18, pages 10443-10448, see entiere document.	1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
13 MARCH 1999	31.03.99
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JOSEPH W. RICIGLIANO Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*